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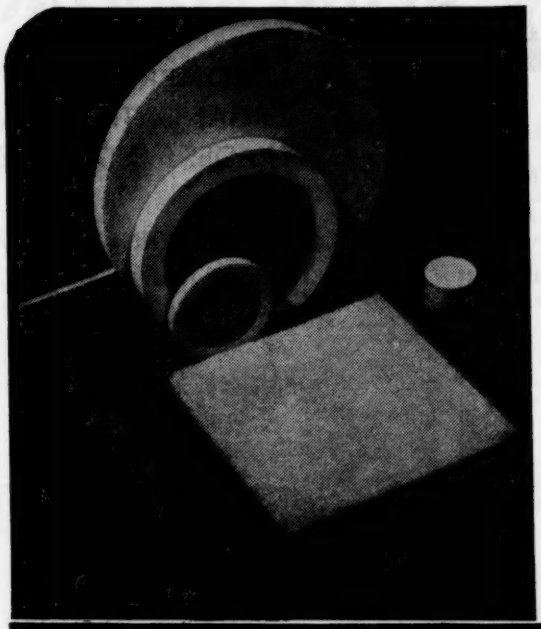

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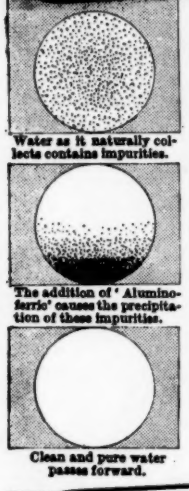

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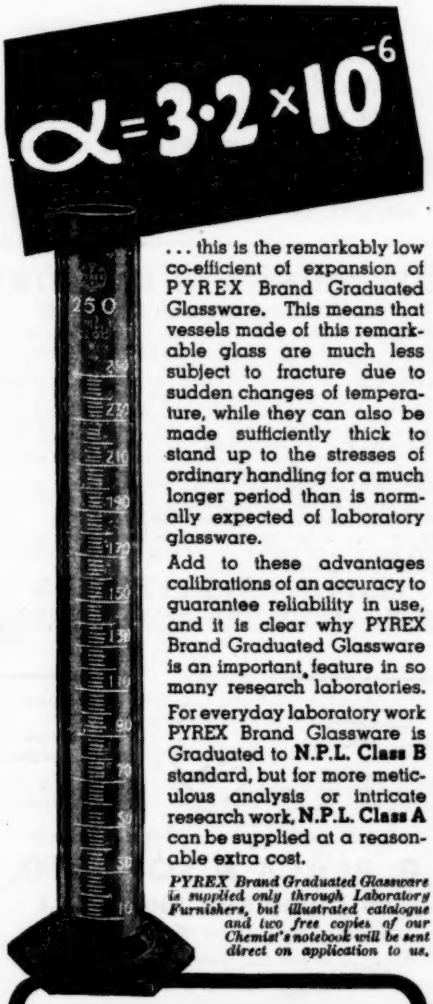

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halogen derivatives of malonanilide and related compounds (*J.*, 1910, **97**, 339); later, he published an oxidative study of papaveraldine with W. H. Perkin, Jun. (*J.*, 1914, **115**, 2013). During the first World War he published some work on intermediates for synthetic local anæsthetics, with A. T. King, and, after joining the staff of British Dyestuffs Corporation Ltd., he engaged in a long period of activity in dyestuffs chemistry, during which he published a number of papers in the Journals of the Chemical Society, the Society of Chemical Industry, and the Society of Dyers and Colourists on the preparation of naphthalene and quinoline derivatives and on the constitutions of dyes. He was active in work on the revision of the Colour Index and its Supplements.

Mason died quite suddenly on September 19th, 1947. While on holiday at Bognor Regis he was called back to London for an important conference, and expired immediately on his return. He leaves a son and daughter of mature age by his first marriage, and a widow and two younger children of his second marriage, to all of whom the profound sympathy of his numerous friends is accorded.

P. C. L. Thorne.

SAMUEL EDWARD SHEPPARD.

1882—1948.

Samuel Edward Sheppard was born on July 29th, 1882, in Catford, London, S.E., and died on September 29th, 1948, in Rochester, New York, U.S.A.

After attending St. Dunstan's College, Sheppard entered University College, London, in 1900, and in 1903 received the degree of B.Sc. by research, submitting a thesis on the theory of the photographic process which involved a repetition of the work of Hurter and Driffield with the use of improved apparatus and the physicochemical methods developed since that work had been done. His first papers were published jointly with C. E. K. Mees in 1903 and dealt with the kinetics of development. After graduation, Sheppard equipped a laboratory in his house, and there continued work on photographic science, publishing a long series of papers jointly with Mees until in 1906 he was awarded the D.Sc. degree for a thesis which was published with that of Mees by Longmans Green and Company in 1907 under the title " Investigations on the Theory of the Photographic Process."

In 1906 Sheppard was awarded an 1851 Exhibition Scholarship for two years and went to Marburg, where he worked with Karl Schaum, a professor of photochemistry and the editor of the *Zeitschrift für Wissenschaftliche Photographie*. Sheppard's work was on the structure in solution of sensitizing dyes and particularly of pinacyanol, the red sensitiser discovered only a short time before by Homolka of the Hoechst Dye Works. The study of the structure and behaviour of dyes like pinacyanol continued to attract Sheppard's attention throughout his entire life. After a year in Germany, Sheppard went to Paris, where he worked with Victor Henri at the Sorbonne on colloid chemistry. The time that Sheppard spent in France and Germany gave him an excellent knowledge of the language and a wide acquaintance with the scientific men of those countries, so that throughout his life he felt himself a citizen of the world and particularly at home in France and Germany.

On his return to England in 1908, Sheppard found himself rather at a loose end, but eventually went to Cambridge and worked in the department of agricultural chemistry, where he studied the colloidal properties of bread doughs.

In 1913 Sheppard was invited to take charge of the sections of physical and colloid chemistry in the new research laboratory organised by C. E. K. Mees for the Eastman Kodak Company. The first five years at Rochester were spent principally on a study of the physicochemical properties of gelatin, and a number of papers were published dealing with the measurement of the viscosity of gelatin solutions, the measurement of the jelly strength and the elastic properties of gelatin jellies, the setting and melting points of gelatins, the drying and swelling of gelatin, and the structure of gelatin in solution, in the jelly, and in the dry state. These early papers deal primarily with the definition of the properties to be measured, with methods of measurement, and with instruments for making the measurements. As soon as the methods were so perfected that reproducibility was possible, it became evident that further progress in the realm of the physical and chemical properties was dependent on the nature of the sample. This work culminated in 1929 in a description of a procedure for making a standard gelatin by methods easily reproduced in the laboratories. A scientifically valuable by-product of this work was the manufacture and consequent availability of such a standard de-ashed gelatin to

laboratories in general, biological as well as chemical. This line of work resulted in a series of papers in 1930 on the structure of sols and gels, papers which, at a time when the basic difference between these systems and ordinary solutions was poorly defined, clarified the differences and were a very helpful contribution to the discussions then occurring in the literature.

During the First World War, the Kodak Research Laboratories were approached by the Submarine Defence Corporation with a problem relating to the use of finely divided coal as a fuel, the material being a waste product from the handling of coal. Sheppard found that, by the use of resin soaps as dispersants, powdered coal could be made into a stable suspension in fuel oil, and this material was utilised on a fairly large scale under the name " colloidal fuel ". The patent that Sheppard obtained for this was assigned to the Submarine Defence Corporation.

After the First World War, Sheppard began to turn his attention to the structure and properties of silver halide emulsions, and his first work took the form of a study of the distribution of the sizes of the silver halide grains in an emulsion, the intention being to work out the relation between this distribution and the sensitometric properties of the material. Thus began a long series of studies that are not yet completed though much progress has been made in the last thirty years. At the same time, working with Dr. Ludwik Silberstein and with Mr. A. P. H. Trivelli, Sheppard began to consider the action of light on the halides and the nature of sensitivity, and about 1923 a series of papers was published on the theory of photographic sensitivity and of exposure, which resulted in the presentation of the concentration speck hypothesis, according to which the sensitivity was related to discontinuities in the silver bromide lattice, presumably due to some foreign substance. At the same time a very notable group of studies was going forward on the measurement of size frequency distribution, which led to the development of microscopic methods by which the grain-size frequency distribution could be measured for practical silver bromide emulsions.

The well known sensitising property of gelatin in the photographic process led to a systematic study of the difference between photographic gelatins in their sensitising power and the nature of the substance in gelatin which conferred sensitivity. By a painstaking series of analyses, it was found that the sensitiser inherent in natural gelatin was concentrated in the liquors obtained by the acid treatment of the raw material after liming, and eventually it was found that the chemical properties of the sensitiser corresponded to those of allylthiourea and that therefore the gelatin sensitiser was essentially one which could produce silver sulphide specks in the silver bromide crystals.

This discovery is perhaps the greatest advance made in Sheppard's scientific career. All further study of the photographic properties of gelatin, of the nature of the sensitivity of silver halides, and of the latent image have been conditioned by it. Its publication won for Sheppard instant recognition. He was awarded the Adelsköld medal of the Swedish Photographic Society in 1929, the progress medal of the Royal Photographic Society in 1928, and the honorary fellowship of the Royal Photographic Society in 1926. In 1928 he delivered the Hurter and Driffield Memorial Lecture to the Royal Photographic Society, and in 1930 received the Nichols Medal of the American Chemical Society.

From that time, Sheppard's scientific work covered a prodigious range of knowledge. Besides the work on the latent image, he studied such matters as the photovoltaic effects—that is, the electrical response of silver halide to light—the colloidal structure of film base materials and their physicochemical and elastic properties, the nature of development, and particularly the nature of dye sensitising, the absorption of sensitising dyes to silver halides, the structure of the layers which they formed, and their sensitising effects.

Sheppard realised that the solution of the problem of dye sensitising would involve not only the coupling of the dye to the silver halide lattice by absorption but an understanding of the nature of the absorption of light by the resonance structure of the dye. Thus he studied the absorption spectra of dyes in various solvents, in vapour phases, and when adsorbed to surfaces. This is the field which was chiefly engaging his attention when his health failed.

The work thus far mentioned has been referred to the central theme, namely, the science of photography. The generalisation of his thought in terms of application to physical and colloid chemistry was characteristic of Sheppard. For example, his studies of the water equilibria of gelatin, the drying and swelling of gelatin, and the nature of the viscosity phenomena, led to allied studies of systems involving other polymeric materials, such as the cellulose esters. His work in viscosity led to the resuscitation of an earlier suggested but forgotten relationship between viscosity and temperature which gives a valuable insight into the nature of viscous flow. This relationship, which was simultaneously rediscovered by Andrade, is now fundamental in any consideration of viscosity. Thoughts on the nature of gelatin solutions,

cellulose ester solutions, and similar colloidal solutions, were probably responsible for his work on the electrophoresis of dispersions of rubber latex and his exceedingly valuable inventions relating to the electro-deposition of rubber. It is an interesting commentary on the diversity of his scientific work that the investigation on rubber came to its climax almost simultaneously with his discovery of the sensitising materials in gelatin.

While never robust, Sheppard enjoyed good health until a few years ago, when he began to have trouble with his eyes, which culminated in the loss of one eye from glaucoma. At the same time, his heart was affected and continued to fail until in January 1948 he found it necessary to resign from his position with the Kodak Company.

In 1912 Sheppard married Miss Eveline Lucy Ground; she and a son, Samuel Roger, survive him.

Sheppard's scientific career offers a contrast to that of many of his colleagues in the academic laboratories of the world. Very early in his life he became associated with an industrial laboratory, at a time when industrial laboratories were often chiefly analytical laboratories devoted to process control. But this association with technology did not only result in inventions and discoveries of great value to the art of photography, but also in a series of publications in the scientific papers of the world, papers which have ranged widely over many of the branches of physical and colloid chemistry. The rich diversity of his work may be ascribed to the conjunction of two circumstances: the driving curiosity which he possessed, fundamental in a scientist, and the complex art of photography, which, not only in its primary phenomena but in most of its associated procedures, was replete with facts for which the current knowledge had no explanation. Particularly among scientists of recent days one sees men whose whole life is spent with one technique, with the elaboration and enlargement of knowledge in one field, but photography took Dr. Sheppard from gelatin and biochemistry to latent image and quantum theory, from plasticity and cellulose esters to dyes and absorption spectra.

More than any other single worker, Sheppard has been responsible for our present knowledge of the theory of the photographic process. He explored every section of the chemistry of that process, and everywhere his studies brought light.

C. E. K. Mees.

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62. *A New Route to Iminazoles: Synthesis of 2-ω-Aminoalkyl Derivatives of 4-Methyliminazole.*

By L. P. Ellinger and A. A. Goldberg.

A new synthesis of the iminazole heterocyclic system by condensation of iminoethers with α-aminocarbonyl compounds is described.* 2-ω-Aminoalkyl derivatives of 4-methyliminazole have been prepared from ω-acylamidoalkylcarboxylic iminoethers and aminoacetone followed by deacylation of the 4-methyl-2-ω-aminoalkyliminazoles thus produced.

These analogues of histamine were prepared for examination for vaso-dilating and broncho-constricting activity.

Difficulties associated with the preparation of histamine—4-(2-aminoethyl)iminazole—led to a search for more accessible analogues which might possess similar pharmacological properties. 1-(2-Aminoethyl)iminazole has been prepared by Lur'e, Kuleshova, and Kochetov (*J. Gen. Chem. Russia*, 1939, **9**, 1933), but since this is an *N*-substituted iminazole it is not a true analogue of histamine. Accordingly methods were devised for the synthesis of the unknown 2-(2-amino-ethyl)iminazole and its homologues; availability of intermediates limited the work in the first instance to the preparation of the corresponding derivatives of 4-methyliminazole.

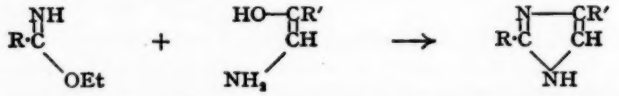
Attention was first directed to the classical method of forming the iminazole system by condensation of amidines with α-halogeno-carbonyl compounds (Kunckell, *Ber.*, 1901, **34**, 637) but, under all the varied reaction conditions employed, benzamidoacetamidine and chloro-acetone failed to give the desired iminazole. Similarly interaction of benzamidoacetamidine with αβ-dibromoethylene in presence of an acid acceptor did not yield the iminazole; contrast the condensation of amidines and trimethylene dibromide with production of dihydropyrimidines (Pinner, *Ber.*, 1893, **26**, 2122, 2124).

The synthesis of the pyrimidine nucleus by condensation of (aminomethylene)malononitrile and ethyl (aminomethylene)cyanoacetate with (i) thioamides (Wuest and Hoffer, U.S.P. 2,271,503; Kenner, Lythgoe, Todd, and Topham, *J.*, 1943, 388; B.P. 546,624) and with (ii) iminoethers

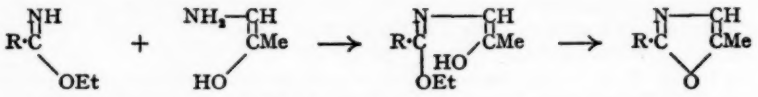
* The new synthesis of iminazoles was developed in 1946 and forms the subject matter of B.P. 27,427/46 (filed September 12th, 1946).

(B.P. 486,414; Hromatka, D.R.-P. 667,990) and also the synthesis of iminazolines by condensation of iminoethers with ethylene diamine (B.P. 529,055; F.P. 671,362; Klaver and Urech, *Helv. Chim. Acta*, 1944, **27**, 1762) suggested two new possible routes to the iminazole system by substitution of an α-aminocarbonyl for the α-aminomethylene compound. It was found that, while the aminoacetone failed to react in the designed manner with benzamidothioacetamide, it condensed satisfactorily with benzamidoacetiminoethyl ether under carefully controlled conditions to yield **4-*methyl*-2-*benzamidomethyliminazole***. Similarly, aminoacetone and β-benzamidopropioniminoethyl ether yielded **4-*methyl*-2-(2-*benzamidoethyl*)*iminazole***.

It would appear that the synthetic route



is novel and of general applicability for the preparation of 2-substituted iminazoles; the requisite iminoethers R·C(:NH)·OEt are readily accessible from the cyanides RCN and various α-aminocarbonyl compounds, including aminoacetaldehyde, are available in the form of their salts. Condensation of α-aminocarbonyl compounds and iminoethers takes place only between the free bases and it is necessary to employ anhydrous conditions to restrict formation of amide from the iminoether. In the two cases investigated the yields of the desired iminazoles were of the order of 40%, and it is probable that the factors which reduce yield are (i) interaction of the iminoether with the solvent (alcohol) to form ortho-ester, (ii) self-condensation of the aminoacetone base to give 2 : 5-dimethyl-1 : 4-dihydropyrazine, and (iii) condensation of the aminoacetone with the iminoether by elimination of ammonia and production of the *N*-acetonyliminoether (reverse condensation) which by loss of alcohol can cyclise to the 2-substituted oxazole (cf. Cornforth, *J.*, 1947, 96).



In order to limit formation of dihydropyrazine it was found expedient to mix the stable aminoacetone hydrochloride (1 mol.) with the iminoether base (1 mol.) and release the base of the former by the portionwise addition of alcoholic sodium ethoxide (1 mol.). Even at temperatures well below 0°, however, considerable quantities of ammonia were developed signifying progress of the " reverse " condensation.

Isolation of the 4-methyl-2-benzamidoalkyliminazoles from the reaction mixture was facilitated by their solubility in cold dilute mineral acid and their insolubility in cold acetone. Hydrolysis was effected by boiling 5N-hydrochloric acid to give **4-*methyl*-2-*aminomethyliminazole*** and **4-*methyl*-2-(2-*aminoethyl*)*iminazole*** which were isolated in the form of their ***dihydrochlorides***. In both cases the free base was a viscid oil which resisted distillation and analysis owing to hygroscopicity and affinity for atmospheric carbon dioxide. By condensation of the free bases with 5 : 8-dichloro-3-methoxyacridine in the presence of phenol they were converted respectively into (8-*chloro*-3-*methoxy*-5-*acridylamino*)-(4-*methyl*-2-*iminazolyl*)*methane* and 1-(8-*chloro*-3-*methoxy*-5-*acridylamino*)-2-(4-*methyl*-2-*iminazolyl*)*ethane* which are both well-defined crystalline compounds suitable for analysis. Attention is drawn to the utility of 5 : 8-dichloro-3-methoxyacridine as a reagent for identifying primary amines since the formation of the derivative is facile, the weight is increased, and the products are usually well defined with reasonably high melting points containing both halogen and nitrogen. The iminazole nucleus appears not to condense with the reagent under the conditions selected.

The physiological properties of these new analogues of histamine will be reported elsewhere.

Experimental.

4-*Methyl*-2-*benzamidomethyliminazole*.—Benzamidoacetiminoethyl ether hydrochloride (Goldberg and Kelly, *J.*, 1947, 1374; 128 g.; 0·5 mol.) was added portionwise during 10 minutes to a stirred solution of sodium (0·65 mol.; 15·2 g.) in anhydrous alcohol (400 c.c.) at −5°. After a further 15 minutes a solution of aminoacetone hydrochloride (0·5 mol.; 54 g.) in anhydrous alcohol (200 c.c.) was added dropwise during ½ hour, the mixture stirred at −5° for a further 1 hour and then allowed to stand at room temperature for 24 hours. The mixture was again cooled to −5° and a solution of sodium (7·7 g.; 0·35 mol.) in anhydrous alcohol (150 c.c.) added with stirring during 1 hour. After keeping at room temperature for 3 days the insoluble material was removed and the filtrate evaporated to dryness at reduced pressure. The gummy residue was dissolved in boiling acetone (100 c.c.), the solution filtered (charcoal) and allowed

to stand on ice, *4-methyl-2-benzamidomethyliminazole* separating as a microcrystalline powder; this was collected, triturated with cold acetone (60 c.c.), drained, and dried at low temperature (yield, 32·5 g.; m. p. 184—186°). The acetone mother-liquors and washings were evaporated to dryness at reduced pressure, the residual gum dissolved in cold 2N-hydrochloric acid (120 c.c.) and the solution kept on ice for several hours. The crystalline precipitate (A) was removed and the filtrate basified with saturated aqueous sodium carbonate. The oil which separated crystallised on keeping for 48 hours in the ice chest; this, on recrystallisation from boiling acetone (50 c.c.), gave a further amount (13 g.) of 4-methyl-2-benzamidomethyliminazole, m. p. 184—186° (total yield, 45·5 g.; 42%). For analysis a sample was recrystallised from acetone and obtained in colourless prisms, m. p. 185—186° (Found: C, 66·8; H, 6·1; N, 19·8. $C_{12}H_{13}ON_3$ requires C, 67·0; H, 6·0; N, 19·5%).

The *by-product* which separated from the cold HCl solution (A) crystallised from acetic acid in colourless plates (6·5 g.), m. p. 238—240°, which were insoluble in cold dilute mineral acid and in alkali (Found: N, 12·9. $C_{12}H_{12}O_2N_2$ requires N, 13·0%). This was not further investigated.

4-Methyl-2-aminomethyliminazole.—The foregoing benzamido-compound (32·5 g.) was refluxed with 5N-hydrochloric acid (320 c.c.) for 4 hours, the solution chilled, the precipitate of benzoic acid removed, and the filtrate evaporated to dryness at 50° at reduced pressure. The residue was dissolved in the minimum amount of boiling water (15 c.c.), alcoholic hydrogen chloride (4% w/w; 200 c.c.) added, and the solution stood in the ice-chest; *4-methyl-2-aminomethyliminazole dihydrochloride* (21 g.; 75%) slowly separated in large colourless prisms, m. p. 248—250° (Found: C, 31·9; H, 5·6; N, 24·0; Cl, 38·2. $C_5H_9N_3,2HCl$ requires C, 32·6; H, 6·0; N, 22·8; Cl, 38·6%).

The foregoing dihydrochloride (15·3 g.) was refluxed with a solution of sodium (3·5 g.) in anhydrous methyl alcohol (60 c.c.) for 15 minutes. After sodium chloride and solvent had been removed 4-methyl-2-aminomethyliminazole was obtained in theoretical yield as a gum. On attempted distillation the bulk decomposed; on mixing an alcoholic solution of the small distillate with a slight excess of alcoholic hydrogen chloride, the dihydrochloride separated in colourless prisms, m. p. 246° alone and in admixture with the sample described below.

A mixture of 2-aminomethyl-4-methyliminazole dihydrochloride (0·94 g.) was refluxed with a solution of sodium (0·23 g.) in anhydrous alcohol (20 c.c.) for 5 minutes, the sodium chloride removed, and a hot solution of *p*-nitrobenzoic acid (3·0 g.) in alcohol (30 c.c.) added; on cooling, *4-methyl-2-aminomethyliminazole di-p-nitrobenzoate* (2·2 g.) separated. For analysis it was recrystallised twice from alcohol and obtained in slender needles, m. p. 190—192°, with sintering at 186° (Found: C, 51·0; H, 4·2; N, 16·0. $C_5H_9N_3,2C_7H_5O_4N$ requires C, 51·2; H, 4·3; N, 15·7%).

(8-Chloro-3-methoxy-5-acridylamino)-(4-methyl-2-iminazolyl)methane.—A solution of 5 : 8-dichloro-3-methoxyacridine (7·5 g.) in phenol (50 g.) was heated to 115° for 15 minutes and then a solution of 4-methyl-2-aminomethyliminazole (4·3 g.) in phenol (30 c.c.) added with shaking. The solution was heated to 115° (internal) for 6 hours, cooled, and poured into an excess of anhydrous ether. After standing overnight the yellow precipitate (11 g.) was collected, dried over sulphuric acid, and then shaken with an excess of cold 2·5N-sodium hydroxide and glass beads for 2 hours. The free base (9·0 g.) was collected, washed well with cold water until free from alkali, and crystallised twice from dilute alcohol. The *derivative* separated in small yellow tablets, m. p. 150—154° (Found: N, 15·7; Cl, 10·0. $C_{19}H_{17}ON_4Cl$ requires N, 15·9; Cl, 10·1%).

4-Methyl-2-(2-benzamidoethyl)iminazole.—Crude β-benzamidopropioniminoethyl ether hydrochloride (Goldberg and Kelly, *loc. cit.*), from β-benzamidopropionitrile (20 g.), was suspended in benzene (60 c.c.), and this suspension added rapidly to a stirred solution of sodium (3·6 g.) in anhydrous alcohol (80 c.c.) at −5°. After a further 10 minutes a solution of aminoacetone hydrochloride (10·8 g.) in anhydrous ethyl alcohol (150 c.c.) was added dropwise during a period of 1½ hours with rapid stirring at −5°. The mixture was left for 24 hours on ice, cooled again to −5°, and a solution of sodium (1·0 g.) in anhydrous alcohol (30 c.c.) added with stirring; the suspension was then kept on ice for 48 hours and finally for a further 24 hours at room temperature. The precipitate of sodium chloride was removed, the filtrate distilled to dryness at reduced pressure at 30° and the residue dissolved in 2N-hydrochloric acid (50 c.c.). After being kept in the ice-chest overnight the small precipitate was removed and the filtrate basified with concentrated aqueous sodium carbonate; the oil which precipitated crystallised on being kept at 0°. This was separated and redissolved in 2N-hydrochloric acid, the solution filtered, and the base reprecipitated with sodium carbonate solution. The solid thus obtained was ground with hot acetone (150 c.c.), the mixture kept on ice for 12 hours, and the undissolved microcrystalline *4-methyl-2-(2-benzamidoethyl)iminazole* (7·2 g.; m. p. 204—206°) drained and dried at low temperature. A sample crystallised from a large volume of boiling acetone in small colourless needles, m. p. 206—208° (Found: C, 68·2; H, 6·5; N, 18·4. $C_{13}H_{15}ON_3$ requires C, 68·1; H, 6·5; N, 18·3%).

4-Methyl-2-(2-aminoethyl)iminazole.—The foregoing benzamido-compound (5 g.) was refluxed with 5N-hydrochloric acid (50 c.c.) for 4 hours. After being chilled, the benzoic acid (2·1 g.) was removed and the filtrate evaporated almost to dryness at reduced pressure. The residue was dissolved in the minimum amount of hot water (3 c.c.), alcoholic hydrogen chloride (2% w/w; 60 c.c.) added, and the solution chilled; *4-methyl-2-(2-aminoethyl)iminazole dihydrochloride* (3·7 g.) separated in colourless plates, m. p. 260—262°. A sample for analysis crystallised from the same solvent in colourless plates, m. p. 262—264°, with sintering at 258° (Found: N, 22·2; Cl, 35·3. $C_6H_{11}N_3,2HCl$ requires N, 21·2; Cl, 35·8%).

The dihydrochloride (1·0 g.) was added to a solution of sodium (0·23 g.) in alcohol (25 c.c.). The precipitate of sodium chloride was removed and the filtrate mixed with a hot solution of *p*-nitrobenzoic acid (2·7 g.) in alcohol (25 c.c.) and refrigerated for 24 hours, *4-methyl-2-(2-aminoethyl)iminazole di-p-nitrobenzoate* separating in large pale yellow transparent prisms, m. p. 164—166°. A sample recrystallised several times from alcohol had m. p. 180—182° (Found: C, 52·5; H, 4·5; N, 15·1. $C_6H_{11}N_3,2C_7H_5O_4N$ requires C, 52·3; H, 4·6; N, 15·3%).

1-(8-Chloro-3-methoxy-5-acridylamino)-2-(4-methyl-2-iminazolyl)ethane.—A solution of 5 : 8-dichloro-3-methoxyacridine (8·0 g.) and 4-methyl-2-(2-aminoethyl)iminazole (4·5 g.; isolated from the dihydrochloride in the manner described for the lower homologue) in phenol (80 g.) was heated at 112—115° (internal temp.) for 6 hours and then poured into excess of anhydrous ether. After standing overnight

the precipitate was collected, converted into the base by grinding with cold 2·5N-sodium hydroxide, and the *base* (9·0 g.) collected, washed free from alkali, and recrystallised three times from dilute pyridine. The product separated in yellow microcrystalline aggregates, m. p. 106—112° decomp. (Found in material dried over phosphoric oxide at 20°/1 mm. for 30 days: N, 15·2; Cl, 9·6. $C_{20}H_{19}ON_4Cl$ requires N, 15·3; Cl, 9·7%).

Phthalimidoacetone.—The method described by Fourneau ("Organic Medicaments and their Preparation", trans. Silvester, 1925, p. 210) for the preparation of chloroacetone gave poor yields owing to the use of insufficient water and calcium carbonate. The following modification of the procedure gave consistent yields of 60—65% of redistilled monochloroacetone. Marble chips the size of grains of maize (500 g.; 5 mols.) were covered with industrial grade acetone (580 g.; 733 c.c.; 10 mols.) and the mixture heated to the boiling point. External heating was discontinued and a current of dry chlorine passed in through a sintered-glass gas distributor at a rate of 1·25—1·30 g. of chlorine per minute for 9½ hours during which time water (240 c.c.; 13·3 mols.) was added dropwise at a uniform rate. The reaction started rapidly and the heat generated was sufficient to maintain the reaction temperature at *ca.* 60° throughout. At the end of this period the marble had completely disappeared and the weight of the mixture had increased by 630 g., *i.e.* 86% of the theoretical. The mixture was cooled, water (200 c.c.) *immediately* added in order to prevent crystallisation of calcium chloride dihydrate, and the lower aqueous layer removed. The chloroacetone layer was washed with water (200 c.c.), dried overnight over calcium chloride, then for a further 3 hours over fresh calcium chloride, and distilled through an 8 in. Vigreux column. This gave the following fractions: (*a*) 185 g., b. p. 114°/745 mm.; (*b*) 525 g., b. p. 114—117°/745 mm., together with 30 g. of residue. Fraction (*a*) was redistilled to yield: (*aa*) 99 g., b. p. 114°/745 mm., and (*ab*) 77 g., b. p. 114—117°/745 mm., together with 6 g. of residue. Fractions (*b*) and (*ab*) were combined and refractionated to yield 564 g. of pure chloroacetone as a colourless oil, b. p. 116—118°/745 mm., after rejection of a head fraction of 15 g., b. p. 116°/745 mm. The uniformly high yields of phthalimidoacetone from this material indicate its purity.

Chloroacetone (92·5 g.), potassium phthalimide (150 g.), and xylene (160 c.c.) were heated at 125—130° (bath temp.) for 1½—2 hours. The xylene was removed by steam-distillation, the residual solid drained and dissolved in boiling alcohol (400 c.c.), and the small amount of inorganic material removed and washed into the filtrate with boiling alcohol (50 c.c.). The filtate was brought to the b. p., boiling water (360 c.c.) added, and the filtered (charcoal) solution allowed to cool. Phthalimidoacetone (138 g.) separated in flat pale yellow prisms, m. p. 118—120°.

Aminoacetone Hydrochloride (cf. Gabriel, *Ber.*, 1893, **26**, 2197; 1902, **35**, 3807).—Crude phthalimidoacetone (203 g.) was refluxed with 7N-hydrochloric acid (1250 c.c.) for 2 hours (oil-bath). The mixture was allowed to cool in order that phthalic acid could crystallise and then reheated to the reflux temperature for a further 2 hours. (If the solution was not cooled after the initial heating it was invariably found that the phthalic acid crystallised at the b. p. with considerable violence.) The mixture was cooled, the phthalic acid (180 g.) removed, and the filtrate evaporated to complete dryness at reduced pressure at 40—50°. The residue was heated with alcohol (200 c.c.) and 3N-alcoholic hydrogen chloride (20 c.c.) and the insoluble ammonium chloride rapidly filtered off and washed with boiling alcohol (50 c.c.) into the filtrate which was then evaporated again to complete dryness at reduced pressure at 50°. This treatment was repeated, the filtrate concentrated to small volume (*ca.* 90 c.c.), and the solution chilled. Addition of anhydrous ether (120 c.c.) with shaking effected rapid crystallisation of the aminoacetone hydrochloride which was immediately filtered off, washed with anhydrous ether, and dried in a vacuum over sulphuric acid (yield, 74 g. of nearly white needles, m. p. 80°).

Benzamidoacetone.—A solution of the foregoing amine hydrochloride (44 g.) in water (100 c.c.) was added dropwise during ¾ hour to a rapidly stirred mixture of sodium carbonate (44 g.), water (200 c.c.), and benzoyl chloride (60 c.c.) at 5—10°; during this period a solution of sodium carbonate (44 g.) in water (100 c.c.) was simultaneously added at such a speed that the pH of the mixture was maintained between 8·0 and 10·0. After the addition of a further amount of benzoyl chloride (6 c.c.) the mixture was stirred at room temperature for 4 hours and chilled, the solid collected, drained on porous pot, and extracted with boiling benzene (2 × 200 c.c.). Benzene was distilled from the filtrate until the solution had a volume of *ca.* 150 c.c., the latter cooled, diluted with ligroin (100 c.c.; b. p. 60—80°) and chilled. The benzamidoacetone rapidly separated as a mass of crystals which were collected and dissolved in benzene (225 c.c.) and the filtered solution chilled and diluted with ligroin (150 c.c.; b. p. 60—80°); the solution was seeded, diluted with a further amount of ligroin (50 c.c.), and allowed to stand overnight. The compound (36 g.) separated in glistening nacreous flakes, m. p. 84° (Found: N, 8·1. Calc. for $C_{10}H_{11}O_2N$: N, 7·9%). It is slightly soluble in water; at 30° the saturated aqueous solution contains *ca.* 7 g. of benzamidoacetone per litre; when this solution is stirred and saturated with sodium chloride the compound separates in nacreous flakes (4·8 g.).

The 2 : 4-*dinitrophenylhydrazone* separated from a mixture of aqueous alcohol, pyridine, and dioxan in small orange prisms, m. p. 218—220° (Found: N, 19·4. $C_{16}H_{15}O_5N_5$ requires N, 19·6%). It is soluble in pyridine but almost insoluble in alcohol.

The *thiosemicarbazone* separated from dilute alcohol in glittering colourless plates, m. p. 220—222° (Found: N, 22·4; S, 12·7. $C_{11}H_{14}ON_4S$ requires N, 22·4; S, 12·8%).

The *oxime* crystallised from boiling water in glittering colourless leaves, m. p. 132—134° (Found: N, 14·8. $C_{10}H_{12}O_2N_2$ requires N, 14·6%).

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[*Received, April 26th*, 1948.]

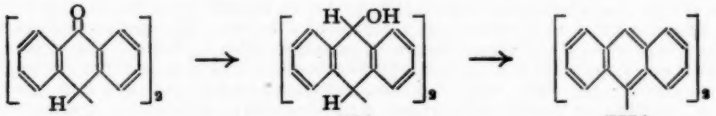
63. *The Symmetrical Dianthryls. Part I.*

By F. Bell and D. H. Waring.

The preparation of 9 : 9′-dianthryl has been studied in detail and new methods devised. 1 : 1′-*Dianthryl* is described and compared with 2 : 2′- and 9 : 9′-dianthryls.

The literature on 9 : 9′-dianthryl is considerable but inconsistent. Schulze (*Ber.*, 1885, **18**, 3035) first prepared the hydrocarbon, m. p. 300°, by the dehydration of anthrapinacol by acetyl chloride in a sealed tube. Liebermann and Gimbel (*Ber.*, 1887, **20**, 1854) state that it can be obtained by the reduction of anthraquinone with tin and hydrochloric acid. This method was adopted by Eckert and Hofmann (*Monatsh.*, 1915, **36**, 497) who state, however, that a little platinic chloride should be added to the mixture. Some time later Barnett and Matthews (*J.*, 1923, **123**, 380) reported failure to produce 9 : 9′-dianthryl by reduction of anthraquinone, but, by reduction of anthrone in acetic acid with zinc and hydrochloric acid, obtained a hydrocarbon crystallising in colourless needles, m. p. above 360°, to which they ascribe this constitution. They attribute previous low melting points to impurities, as shown by the yellow colour recorded in the descriptions.

Schlenk and Bergmann (*Annalen*, 1928, **463**, 165), by the interaction of sodiodiphenylmethane and 9-bromoanthracene, obtained in small yield a 9 : 9′-dianthryl, m. p. 304°, depressed by admixture with Barnett and Matthews's compound. The isomerism of these hydrocarbons was attributed to a non-planar arrangement of the anthracene system (see also, *idem*, *Ber.*, 1929, **62**, 745). Subsequently, however, Bergmann and Schuchardt (*Annalen*, 1931, **487**, 244) state that Barnett and Matthews's method yields a product, m. p. 302°. The compound of high



(I.) (II.) (III.)

melting point is regarded by them as a dehydrogenation product produced by use of a high boiling solvent for the recrystallisation of the 9 : 9′-dianthryl—in our view a most improbable explanation. Clar (*Ber.*, 1932, **65**, 518), in agreement with Bergmann and Schuchardt, states that Barnett and Matthews's method yields a product, m. p. 308—310°, identical with that obtained by the reduction of anthraquinone with tin. Previous difficulties in the reduction of anthraquinone are attributed by him to the use of pure tin. Clar uses plumber's tin (löt Zinn). In spite of this Dufraisse, Vellus, and Vellus (*Bull. Soc. chim.*, 1938, **5**, 600) dispute the correctness of the tin reduction method and state that it is necessary first to prepare anthrone and then reduce this.

In the meantime Minaev and Fedorow (*Ber.*, 1929, **62**, 2489) recorded the preparation of 9 : 9′-dianthryl, m. p. 300°, by the hydrolysis of the monosulphonic acid, obtained by the interaction of 9-nitroanthracene with sodium sulphite, and Barnett and Goodway (*J.*, 1929, 813) the preparation of a pale yellow " *iso*dianthryl ", m. p. 312°, by the interaction of anthrone with benzhydryl chloride and subsequent reduction of the benzhydrylanthrone.

Most of these previous experiments have been repeated, and 9 : 9′-dianthryl can now be obtained consistently by any of the following processes :

(i) Reduction of anthraquinone with ordinary tin and fuming hydrochloric acid. Use of plumber's tin or addition of platinic chloride secures no advantage;

(ii) Reduction of anthrone in glacial acetic acid with either zinc or tin and hydrochloric acid;

(iii) Conversion of 9-bromoanthracene into the Grignard reagent and decomposition of this with cupric chloride;

(iv) Interaction of sodiodiphenylmethane with 9-bromoanthracene. The main product is anthracene;

(v) Interaction of sodiotriphenylmethane with 9-bromoanthracene;

(vi) Clemmensen reduction of 9 : 9′-dianthronyl (I) to 10 : 10′-*dihydroxy*-9 : 10 : 9′ : 10′-*tetrahydro*-9 : 9′-*dianthryl* (II) which is easily dehydrated to 9 : 9′-dianthryl (III) by boiling with phosphoric oxide in toluene. Dehydration could not be brought about by acetic anhydride which yielded anthracene and anthranyl acetate;

(vii) Reduction of benzhydrylanthrone.

9 : 9′-Dianthryl, obtained by all of these processes, formed colourless plates, m. p. 308°, from

acetic anhydride and yielded additive *products* with toluene and pyridine. It did not combine with either maleic anhydride or benzoquinone but reacted readily with lead tetra-acetate to give dianthranol diacetate.

An attempt to extend method (vi) to the preparation of other dianthryls was unsuccessful. 1 : 4 : 1′ : 4′-Tetramethyl-9 : 9′-dianthronyl on Clemmensen reduction gave only 1 : 4-dimethylanthracene. Method (ii), which gives the highest yield of 9 : 9′-dianthryl, is also of limited application since 1 : 4-dimethylanthrone could not be reduced further by the process. The effect appears to be of a steric nature (cf. Barnett, *Ber.*, 1932, **65**, 1563).

The only reference to 2 : 2′-dianthryl is in a paper by Scholl (*Ber.*, 1919, **52**, 1834) who prepared it by the distillation of tetrahydroxy-2 : 2′-dianthraquinolyl with zinc dust. His results are confirmed and the slight possibility that the product might be 1 : 1′-dianthryl is now ruled out by the preparation of the latter hydrocarbon.

Previous attempts to prepare 1 : 1′-dianthryl proved unsuccessful owing to certain inherent difficulties. 1-Chloroanthracene is attacked by copper only at high temperature and then yields anthracene and, further, 1 : 1′-dianthraquinolyl on distillation with zinc dust or treatment with phosphorus and hydriodic acid yields only *meso*naphthodianthrone (Scholl, *loc. cit.*). However, Scholl and Turner (*Annalen*, 1923, **433**, 163) have described the preparation of 1 : 1′-dianthryl-2 : 2′-dicarboxylic acid by the reduction of 1 : 1′-dianthraquinonyl-2 : 2′-dicarboxylic acid and this has now been decarboxylated to yield 1 : 1′-dianthryl.

Experimental.

(Analyses are by Drs. Weiler and Strauss, Oxford. M. p.s are uncorrected.)

9 : 9′-*Dianthryl.*—(a) *Reduction of anthraquinone.* Anthraquinone (m. p. 277—280°; 10 g.), granulated tin (40 g.), and glacial acetic acid (120 c.c.) were boiled under reflux, and fuming hydrochloric acid (60 c.c.) added a little at a time over a period of 2 hours. The anthraquinone soon passed into solution and crystals of 9 : 9′-dianthryl began to separate after 1½ hours. The heating was continued until the solution on cooling did not deposit any needles of unchanged anthraquinone (total time about 4 hours). After cooling, the flaky solid (5 g.) was separated and crystallised first from toluene (50 c.c.) and then from pyridine or acetic anhydride. 9 : 9′-Dianthryl crystallises from pyridine or toluene with 1 molecule of solvent of crystallisation (Found, in material crystallised from pyridine: loss, 18·0. $C_{28}H_{18},C_5H_5N$ requires loss, 18·2%. Found, in material crystallised from toluene: loss, 20·75%. $C_{28}H_{18},C_7H_8$ requires loss, 20·7%). The solvent-free compound, obtained from acetic anhydride, forms colourless plates, m. p. 308°.

(b) *Reduction of anthrone with zinc.* Anthrone (20 g.), granulated zinc (20 g.), and acetic acid (100 c.c.) were heated under reflux for 8 hours, fuming hydrochloric acid (40 c.c.) being added slowly during the first 5 hours. Crystals of 9 : 9′-dianthryl began to separate after 1 hour. Yield, 8 g. (44%).

(c) *Reduction of anthrone with tin.* Anthrone (10 g.) was dissolved in a mixture of acetic acid (100 c.c.) and fuming hydrochloric acid (40 c.c.) and to the boiling solution granulated tin (40 g.) was cautiously added. Crystals began to separate after a few minutes and the refluxing was continued for 1½ hours. Yield, 4·6 g.

(d) *From 9-bromoanthracene.* The Grignard reagent from 9-bromoanthracene (11·25 g.), magnesium turnings (1·2 g.), and ether (200 c.c.) was decomposed with anhydrous cupric chloride (6·5 g.). The mixture was refluxed for 8 hours, the ether distilled off, and the residue decomposed with ice and acidified with hydrochloric acid. The solid material was filtered off, dried, extracted with alcohol and ether to remove soluble impurities, and the final residue recrystallised from toluene yielding 4·5 g. of 9 : 9′-dianthryl. The main by-product was anthracene.

(e) *Dehydration of 10 : 10′-dihydroxy-9 : 10 : 9′ : 10′-tetrahydro-9 : 9′-dianthryl.* This compound (see below) (0·5 g.) was heated under reflux for 3½ hours in toluene (15 c.c.) with phosphoric oxide (1 g.). The hot solution was filtered, and on cooling yielded pure 9 : 9′-dianthryl.

(f) *Interaction of 9-bromoanthracene with sodiodiphenylmethane.* Results are in accord with those of Schlenk and Bergmann (*loc. cit.*).

(g) *Interaction of 9-bromoanthracene with sodiotriphenylmethane.* 9-Bromoanthracene (8 g.) was shaken for 8 hours with sodiotriphenylmethane (*Org. Synth.*, Coll. Vol. II, 609) (100 c.c.; 17·8%). At the end of this time the red colour had been completely discharged. The mixture was decomposed by addition of water and the solid material filtered off. By crystallisation from xylene it was separated into 9 : 9′-dianthryl (2·38 g.) and anthracene (2·8 g.). The ether layer furnished 10·2 g. of triphenylcarbinol.

It is noteworthy that 9-bromoanthracene could be recovered unchanged when it (10 g.) was heated with sodium powder (10 g.) and anhydrous xylene (200 c.c.) under reflux for 7 hours. It therefore appears possible that changes (f) and (g) are initiated either (i) by the removal of bromine as a positive ion by the negative organic ion or (ii) by a free radical-mechanism involving aerial oxidation of the organic radical to the carbinol.

(h) *Reduction of benzhydrylanthrone* (Barnett and Goodway, *loc. cit.*). The product consists of dianthryl, anthrone, and diphenylmethane. It is probable that the reaction involves a preliminary scission of the compound into anthrone and diphenylmethane.

Reactions of 9 : 9′-Dianthryl.—(a) *With lead tetra-acetate.* 9 : 9-Dianthryl (10 g.) was suspended in a mixture of acetic acid (250 c.c.) and acetic anhydride (5 c.c.) and heated to the boiling point. Crystalline lead tetra-acetate (23 g.) was added over a period of 10 mins. and the heating continued for a

further 30 mins. The solution was filtered from unchanged dianthryl (2·0 g.) and left overnight. The gelatinous red precipitate was filtered off and desiccated (3·3 g., m. p. 255° with darkening). Recrystallised from acetic acid it yielded 1·9 g. of dianthranol diacetate, m. p. 283—284° [hydrolysed to dianthranol, m. p. 230—235°; dibenzoate (yellow powder), m. p. >350°; Barnett, *J.*, 1923, **123**, 380].

(b) *With maleic anhydride.* Equimolecular quantities of maleic anhydride and 9 : 9′-dianthryl were refluxed for 8 hours in the following solvents: xylene, *o*-dichlorobenzene, and nitrobenzene. In all cases the dianthryl was recovered unchanged.

(c) *With benzoquinone.* As (b). No addition product was obtained.

10 : 10′-*Dihydroxy*-9 : 10 : 9′ : 10′-*tetrahydro*-9 : 9′-*dianthryl.*—Dianthronyl (10 g.) was dissolved in dioxan (300 c.c.) in a 1-l. round-bottom flask fitted with a mercury sealed stirrer and reflux condenser. To this solution were added hydrochloric acid (5 c.c.) and the well washed Zn–Hg couple prepared from zinc dust (24 g.) and mercuric chloride (6 g.). The solution was kept at the boiling point for 5 hours, hydrochloric acid (3 c.c.) being added at the end of each hour. The solution was filtered hot and the filtrate poured into 1 litre of water, acidified with hydrochloric acid. After being left overnight the pink precipitate was filtered off and extracted with ethyl alcohol which removed most of the colour, and the residue purified by repeated recrystallisation from acetic acid. 10 : 10′-*Dihydroxy*-9 : 10 : 9′ : 10′-*tetrahydro*-9 : 9′-*dianthryl* forms stout colourless prisms, m. p. 193°; yield, 3 g. (Found: C, 85·7; H, 5·66. $C_{28}H_{22}O_2$ requires C, 86·1; H, 5·64%). 0·5 G. was heated with acetic anhydride (5 c.c.) for 9 hours. On cooling, crystals of anthracene (m. p. 213—214°) separated. The acetic anhydride filtrate, on decomposition with water, deposited fine needles of anthranyl acetate, m. p. 127°. The dihydroxy-compound (0·5 g.) was maintained in the molten state for 1 hour. Some decomposition occurred as shown by slight effervescence and darkening but most of the material was recovered unchanged.

Clemmensen Reduction of 1 : 4 : 1′ : 4′-*Tetramethyldianthronyl.*—This compound, prepared by the method of Barnett (*Ber.*, 1932, **65**, 1563), was reduced by the method employed for dianthronyl. The only product was 1 : 4-dimethylanthracene, m. p. 73—74°, and no trace of less soluble material was obtained.

Reduction of 1 : 4-*Dimethylanthraquinone.*—1 : 4-Dimethylanthraquinone (m. p. 116°; 10 g.) was boiled with acetic acid (150 c.c.) and granulated tin (40 g.). Fuming hydrochloric acid (60 c.c.) was added during 2 hours and the heating continued for a further 3 hours. The yellow solution turned brown and then became colourless; it was filtered hot and left to cool. Pale yellow crystals of 1 : 4-dimethyl-anthrone separated. After recrystallisation from methanol this formed fine needles, m. p. 115° (4 g.).

2 : 2′-*Dimethyl*-1 : 1′-*dianthraquinonyl.*—1-Iodo-2-methylanthraquinone (20 g.) was throughly ground with copper powder (16 g.) and mixed with nitrobenzene (40 c.c.). The mixture was heated under reflux for 7 hours and the nitrobenzene then removed, as far as possible, by steam. The residual solid was filtered off, washed free from nitrobenzene by alcohol; dried, and extracted with sodium dithionite (hydrosulphite) according to the directions of Scholl (*Ber.*, 1907, **40**, 1691). Yield, 5·5 g. (50%). This was converted successively into 1 : 1′-dianthraquinonyl-2 : 2′-dicarboxylic acid (Scholl and Turner, *Annalen*, 1923, **433**, 163) and 1 : 1′-dianthryl-2 : 2′-dicarboxylic acid. The purified acid (Lauer, Oda, and Mijawaki, *J. pr. Chem.*, 1937, **148**, 310; 4·8 g.) was dissolved in dilute (0·5%) sodium hydroxide, and then concentrated (25%) sodium hydroxide added to the hot clear solution until precipitation of the sodium salt began. On cooling the salt (5·2 g.) separated as small white plates.

1 : 1′-*Dianthryl.*—Sodium 1 : 1′-dianthryl-2 : 2′-dicarboxylate (5·2 g.) was intimately mixed with dry lime and the mixture introduced into a long hard-glass test-tube which was closed with a loose plug of glass wool. The tube was heated to dull red for 10 minutes. The grey sublimate was purified by recrystallising three times from xylene. 1 : 1′-*Dianthryl* was obtained as colourless plates, m. p. 321—322°; yield 0·9 g. (Found: C, 95·1; H, 5·1. $C_{28}H_{18}$ requires C, 94·9; H, 5·1%).

2 : 2′-*Dianthryl.*—This was prepared from tetrahydroxy-2 : 2′-dianthraquinonyl by the method of Scholl (*Ber.*, 1919, **52**, 1834) except that the distillation with zinc was conducted under reduced pressure without introduction of hydrogen without any apparent disadvantage. A comparison of the three symmetrical dianthryls is given below:

Dianthryl.	M. p. (uncorr.).	Crystalline form (solvent in parenthesis).	Fluorescence in solution, Benzene and toluene.	Pyridine.	Quinoline.
9 : 9′-	308°	Colourless plates (acetic anhydride)	Pale	Blue	None
1 : 1′-	321—322	Microscopic colourless plates (toluene)	None	Very pale blue	None
2 : 2′-	355	Thick needles (quinoline)	Blue green	Green	Green

Mixed m. p.s (uncorr.): 9 : 9′- + 1 : 1′-Dianthryl 264—272°; 9 : 9′- + 2 : 2′-Dianthryl 290—294°; 1 : 1′- + 2 : 2′-Dianthryl 302—304°.

One of the authors (D. H. W.) is in receipt of a grant from the Department of Scientific and Industrial Research for which he wishes to express his indebtedness.

College of Technology, Belfast. [*Received, May 10th*, 1948.]

64. *Exchange Reactions and Electrolytic Dissociation in Non-aqueous Solvents.*

By C. C. Evans and S. Sugden.

It has been found that the velocity coefficient for the exchange reaction between lithium bromide and alkyl bromides in anhydrous acetone varies with dilution. The similar reaction between sodium iodide and alkyl iodides in methyl alcohol shows no effect on dilution. These results are correlated with the degree of dissociation deduced from conductivity measurements.

In the course of work on exchange reactions of the type $RBr + Br^{*\prime} \rightleftharpoons RBr^{*} + Br^{\prime}$ (where Br^{*} represents a radioactive bromine atom) it was found, with anhydrous acetone as solvent and lithium bromide as the source of bromine ion, that the bimolecular rate constant increased with decreasing concentration of bromide ion. By using radio-bromine activated in the pile at Harwell, it was possible to carry these measurements into very dilute solutions. The first observations were made with *sec.*-octyl bromide at 65·5° and are shown in Table I. In these measurements a = [RBr] was kept nearly constant at 0·044—0·047 g.-mol./l.; b represents [LiBr] in the same units; k_2 is the bimolecular rate coefficient given by

$$k_2 = \frac{1}{t(a+b)} \log_e \frac{1}{1 - x(1 + b/a)/c} \quad \ldots\ldots\ldots \quad (1)$$

where the symbols have the meanings used in earlier papers in exchange reactions (*J.*, 1939, 1279).

Table I.

sec.-Octyl bromide in anhydrous acetone with lithium bromide at 65·5°.

10^4b	2·61	3·02	8·61	15·7	78·0	89·0	150	250	390
10^3k_2	7·21	7·05	4·94	4·15	2·34	2·64	1·59	1·34	1·14

Dippy's observations (*J.*, 1939, 1386) on the conductivity of lithium bromide in anhydrous acetone at 25° indicate that in this solvent lithium bromide is a weak salt with a dissociation constant of the order of 5×10^{-4}. It therefore seemed possible that the effect was due to a more rapid rate of reaction of the bromide ion than the undissociated lithium bromide molecule [later (below) it appeared that the reaction with the undissociated molecule was too slow to be measurable at the temperatures employed]. A series of rate measurements was then made on *n*-butyl bromide and lithium bromide in acetone at 26·2°. This reaction goes at a convenient rate at this temperature and the results can be compared with the conductivity measurements at 25°. In Table II, b = [LiBr], and α was calculated by using $K_{\text{therm.}} = 5{\cdot}22$ (see Appendix). The ratio $10^3k/\alpha$ is roughly constant over a range of concentrations of nearly 400-fold. It has a mean value of 4·6 with a probable error of $\pm 0{\cdot}3$.

If the value of k is expressed as a linear function of α, the method of least squares gives

$$10^3k = 0{\cdot}12 \pm 0{\cdot}05 + (4{\cdot}41 \pm 0{\cdot}17)\alpha$$

This is a test of the "dual mechanism" hypothesis of Acree and his collaborators (see Robertson and Acree, *J. Amer. Chem. Soc.*, 1915, **37**, 1902). The constant term measures the rate of reaction of the undissociated molecule; it appears to be small, and more accurate data are required to determine whether it is significant or not.

Table II.

Velocity coefficient and degree of dissociation.

(*n*-Butyl bromide + lithium bromide in acetone at 26·2°.)

10^4b.	α.	10^3k.	$10^3k/\alpha$.	10^4b.	α.	10^3k.	$10^3k/\alpha$.	10^4b.	α.	10^3k.	$10^3k/\alpha$.
0·504	0·925	3·93	4·3	3·10	0·741	3·57	4·8	79·4	0·314	1·44	4·6
0·595	0·916	3·69	4·0	4·38	0·696	3·48	5·0	153·4	0·257	1·08	4·2
1·28	0·848	3·99	4·7	17·1	0·497	2·56	5·2	191·0	0·241	1·07	4·4
1·53	0·831	4·13	5·0	22·7	0·457	2·22	4·9			Mean	4·6 ± 0·3
2·49	0·774	3·13	4·0	43·4	0·378	1·84	4·9				

As a contrast with this system, the reaction of ethyl iodide with sodium iodide in methyl alcohol at 25° was investigated. This was made possible by the generous gift of 8-day iodine (^{131}I) by the National Institute for Medical Research.

The conductivity of sodium iodide in methyl alcohol at 25° was measured by Thomas and

Marum (*Z. physikal. Chem.*, 1929, **143**, 191). For complete dissociation the Onsager equation gives

$$\Lambda_0 = (\Lambda + b\sqrt{c})/(1 - a\sqrt{c}) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

where Λ is the conductivity at a concentration c. The numerical coefficients were computed by using dielectric constant $D_{25°} = 32{\cdot}7$ (Abegg and Seitz, *ibid.*, 1899, **29**, 242) and viscosity $\eta_{25°} = 4{\cdot}99 \times 10^{-3}$ (I.C.T.); these gave $a = 0{\cdot}8469$, $b = 166{\cdot}2$. This formula is applied to the data of Thomas and Marum in Table III. From the constancy of Λ_0 (calc.) it is concluded that sodium iodide is completely dissociated in methyl alcohol over the range of concentrations studied.

TABLE III.

Limiting conductivity of sodium iodide in methyl alcohol.

10^5c.	Λ.	Λ_0 (calc.).	10^4c.	Λ.	Λ_0 (calc.).	10^4c.	Λ.	Λ_0 (calc.).
0·220	108·6	109·8	1·979	105·3	108·9	3·301	104·0	108·7
0·396	108·2	109·8	1·979	105·2	108·8	8·909	101·3	109·0
0·540	107·9	109·8	2·699	104·5	108·7	10·66	100·9	109·3
1·320	106·2	109·2						

The small drift in the values of Λ_0 (calc.) is probably due to experimental error; if it is interpreted as an incomplete dissociation, $K_{\text{dest.}}$ is greater than 10^{-1}, which at $c = 10^{-4}$ gives $\alpha = 0{\cdot}96$.

The kinetic measurements are given in Table IV. It will be seen that the velocity constant

TABLE IV.

Sodium iodide and ethyl iodide in methyl alcohol at 25°.

($[C_2H_5I] = 0{\cdot}044$ for all solutions; $[NaI] = b$.)

10^4b	2·50	4·60	4·67	9·06	9·10	17·6	22·0	66·5	232
10^5k	8·19	7·61	8·35	8·05	7·91	8·09	8·49	7·90	7·44

Mean 8·0

does not vary with the concentration of sodium iodide. To test whether this reaction is subject to a salt effect, an experiment was carried out with [EtI] = 0·044M, [NaI] = $4{\cdot}26 \times 10^{-4}$N, and $[NH_4ClO_4] = 0{\cdot}059$N. This gave $10^5k = 8{\cdot}24$. From the simple form of the Brönsted theory this reaction involving a neutral molecule should not show a salt effect. This conclusion needs modification when charge distribution in the transition state and orientation of solvent dipoles are considered. Experimentally it would appear that at the concentrations concerned in Tables IV and II salt effects are vanishingly small.

The reaction of *sec.*-octyl bromide in acetone at 65·5° was studied over a wider range of concentrations than those recorded in Table I. The results are represented fairly well by computing α with $K_{\text{therm.}} = 2{\cdot}40 \times 10^{-4}$

$$\log_{10} f^2 = 2\left(23{\cdot}0\alpha c - \frac{4{\cdot}420\sqrt{\alpha c}}{1 + 2{\cdot}116\sqrt{\alpha c}}\right) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

and then taking $10^3k = 11{\cdot}0\alpha$. The coefficients of $\sqrt{\alpha c}$ in the activity-coefficient expression were computed from the dielectric constant at this temperature. Table V shows how well this represents the observed data.

TABLE V.

Rate of reaction of LiBr *with* sec.*-octyl bromide in acetone at 65·5°.*

[LiBr] $\times 10^4$.	α, calc.	10^3k, calc.	10^3k, obs.	Diff., obs. − calc.	[LiBr] $\times 10^4$.	α, calc.	10^3k, calc.	10^3k, obs.	Diff., obs. − calc.
2·61	0·643	7·07	7·21	+0·14	150·0	0·161	1·77	1·53	−0·24
3·02	0·622	6·84	7·05	+0·21	250	0·130	1·43	1·37	−0·06
8·61	0·460	5·06	4·94	−0·12	250	0·130	1·43	1·27	−0·16
15·7	0·379	4·17	4·15	−0·02	390	0·106	1·17	1·14	−0·03
58·0	0·234	2·57	2·34	−0·23	660	0·0822	0·90	0·83	−0·07
78·0	0·209	2·30	2·34	+0·04	760	0·0773	0·85	0·83	−0·02
89·0	0·198	2·18	2·64	+0·46	1390	0·0573	0·63	0·77	+0·14

This can only be regarded as giving a rough estimate of the degree of dissociation of lithium bromide in acetone at 65·5°, but it is of interest since it enables an idea to be obtained of the

order of magnitude of the correction which has to be made to the activation energies previously found for exchange reactions with lithium bromide in this solvent.

Writing $k_{obs.} = \alpha k$, and if E' and E are respectively the uncorrected and the corrected activation energy, we have then

$$E = E' - \mathrm{d}\log_e \alpha/\mathrm{d}(1/T) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

Values of α at the two temperatures and at $c = 10^{-2}$ and 10^{-1} were computed. These gave

$$\Delta \log_e \alpha/\Delta(1/T) = 784 \text{ cals. at } c = 10^{-2} \text{ and } 633 \text{ cals. at } c = 10^{-1}$$

In the concentration range used in most of these exchange reactions the correction is probably less than 1 kcal.

Experimental.

For *sec.*-octyl bromide the rate measurements were made by the method described previously (*J.*, 1939, 1279). For the more volatile butyl bromide and ethyl iodide a modified technique was used. A series of small, sealed ampoules containing known concentrations of reactants was placed in the thermostat and one was removed after a time (t_1) sufficient for it to have attained the desired temperture. Other ampoules were removed at times t_2, t_3, etc. All were treated as follows. The contents of the ampoule, after being cooled in solid carbon dioxide–alcohol, were washed into a flask, cooled in ice-water, and acetone and the alkyl halide removed under vacuum. This required about 20 minutes, and the temperature fell to $-20°$, so that any reaction during this operation could be neglected. The residual lithium bromide (or sodium iodide) was dissolved in a known volume of water, and its radioactivity determined with the solution as an annulus around a thin-walled Geiger–Muller counter connected to a scaling circuit. For the bromide reaction, let $a = [\mathrm{RBr}]$, $b = [\mathrm{LiBr}]$, $x = [\mathrm{RBr}^*]$, $c = [\mathrm{Br}^*]$ initially, then

$$k = \frac{1}{(t_2 - t_1)(a + b)} \log_e \frac{1 - (x_1/c)(1 + b/a)}{1 - (x_2/c)(1 + b/a)}$$

The absolute magnitudes of x and c are not known, but the ratio x/c is given directly by the ratio of the counts, and it is this ratio only which is required. Where necessary correction was made for radioactive decay.

Appendix.

Discussion of Conductivity Data.—The first difficulty encountered in the computation of α from conductivity data is the choice of the limiting conductivity Λ_0. We have attempted a detailed analysis of the available data on the following lines.

For a uni-univalent electrolyte in acetone at 25° the Onsager equation may be written

$$\Lambda_{Ons.} = \Lambda_0 - (1{\cdot}677\Lambda_0 + 338{\cdot}2)\sqrt{\alpha c} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

and the Debye–Hückel approximation for the activity coefficient

$$\log_{10} f \pm = -3{\cdot}732\sqrt{\alpha c}(0{\cdot}1 + 1{\cdot}92\sqrt{\alpha c}) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (6)$$

The numerical coefficients in these equations were computed using dielectric constant $E_{25°} = 20{\cdot}98$ (Graffunder, *Ann. Physik*, 1923, **70**, 225), and viscosity $\eta_{25°} = 0{\cdot}00307$ poise (Thorpe and Rodger, *Phil. Trans.*, 1895, *A*, **185**, 397). In equation (6) the distance of closest approach of the ions was taken as 3×10^{-8} cm. (the sum of the crystal radii is $2{\cdot}96 \times 10^{-8}$). Taking $\alpha = \Lambda/\Lambda_{Ons.}$, we have

$$\Lambda_0 = (\Lambda/\alpha + 338{\cdot}2\sqrt{\alpha c})/(1 - 1{\cdot}677\sqrt{\alpha c}) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (7)$$

The only unknown in this equation is α which was computed as follows:

$$\alpha^2 c/(1 - \alpha) = K_{Ost.} = K_{therm.}/f^2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (8)$$

$K_{therm.}$ was known to be of the order of 5×10^{-4}, and f^2 can be obtained from equation (6). This equation, however, involves α, so with $K_{therm.} = 5{\cdot}0 \times 10^{-4}$, an approximate value of α was inserted in (6) to obtain f. This was used to calculate $K_{Ost.}$ and thence α for a particular value of c. The value of α thus found was inserted in (6) and the series of calculations repeated. This method of successive approximations was continued until the value found for α did not change with further repetitions. The final value of α was inserted in (7) to calculate Λ_0. These calculations were made for the six most dilute solutions measured by Dippy for three values of $10^4 K_{therm.}$, *viz.*, 4·0, 5·0, 6·0. The results are shown graphically in the figure, where the value of Λ_0 calculated is plotted against $\sqrt{c}$. It would be expected that at high dilutions errors introduced by the wrong choice of $K_{therm.}$ or by inadequacy of the expression for f would in the

first approximation vary linearly with $\sqrt{c}$. The straight lines in the figure were obtained by the method of zero sum from the calculated values of Λ_0; the equations to them are :

$$10^4\,K_{\text{therm.}} = 4{\cdot}0;\ \Lambda_0 = 160{\cdot}3 + 480\sqrt{c};\ \text{mean deviation } \pm 0{\cdot}7$$
$$10^4\,K_{\text{therm.}} = 5{\cdot}0;\ \Delta_0 = 160{\cdot}3 + 64\sqrt{c} \quad ,, \quad ,, \quad \pm 0{\cdot}9$$
$$10^4\,K_{\text{therm.}} = 6{\cdot}0;\ \Lambda_0 = 159{\cdot}5 - 174\sqrt{c} \quad ,, \quad ,, \quad \pm 0{\cdot}8$$

From these results it was concluded that $\Lambda_0 = 160{\cdot}0 \pm 0{\cdot}5$ and that $K_{\text{therm.}}$ is a little greater than $5{\cdot}0 \times 10^{-4}$.

This value of Λ_0 was used to compute $K_{\text{therm.}}$ for a more extended series of concentrations, with the results shown in Table VI. The value of α was calculated by successive approximations in the usual manner from the measured conductivities, and the values of $K_{\text{therm.}}$ in col. 4 were computed by using the values of f^2 given by the expression at the head of the Table. Two observations by Blokker (*Rec. Trav. chim.*, 1935, **54**, 975) are included; these are

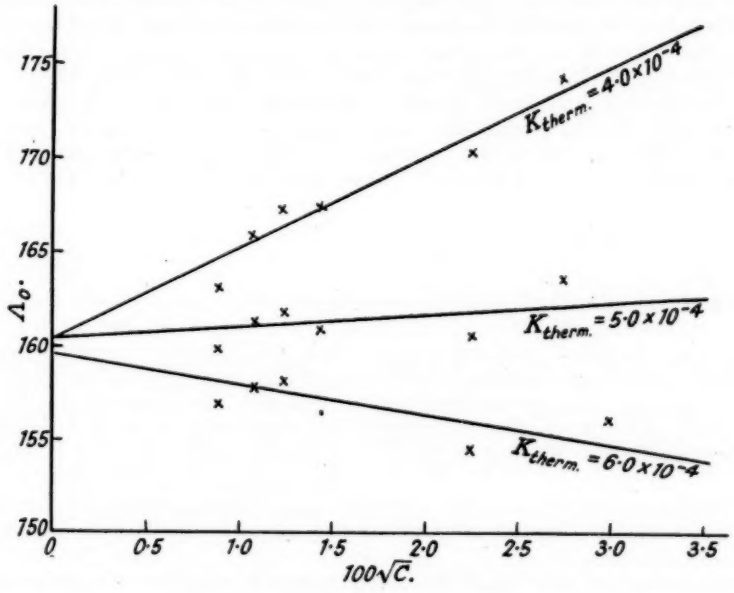


TABLE VI.

Dissociation of lithium bromide in acetone at 25°.

$$E_{\text{Ons.}} = 160{\cdot}0 - 596{\cdot}5\sqrt{ac};\ f^2 = 7{\cdot}464\sqrt{ac}/(1 + 1{\cdot}92/\sqrt{ac}).$$

10^4c.	Λ.	α, cond.	$10^4K_{\text{therm.}}$.	α, calc.	10^4c.	Λ.	α, cond.	$10^4K_{\text{therm.}}$.	α, calc.
0·7663	138·0	0·890	(4·80)	0·897	8·025	88·70	0·604	5·14	0·607
1·148	132·7	0·861	5·18	0·860	20·07	70·4 *	0·499	(5·97)	0·475
1·525	128·0	0·835	5·33	0·832	24·11	62·39	0·444	5·04	0·449
2·057	121·1	0·796	5·13	0·797	33·23	55·51	0·402	4·99	0·409
5·096	100·0	0·671	5·36	0·674	171·7	30·7 *	0·254	5·41	0·250
7·561	91·52	0·622	5·42	0·616					

Mean value of $10^4K_{\text{therm.}}$ (excluding figures in parentheses) = 5·22.

marked with an asterisk. The other observations are due to Dippy (*loc. cit.*). The principal object of these calculations was to determine α. The values of α calculated for $K_{\text{therm.}} = 5{\cdot}22 \times 10^{-4}$ are given in the last column; it will be seen that they are in good agreement with the values deduced from the conductivities up to concentrations of approximately 2×10^{-2}.

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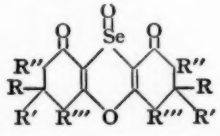
[*Received, May 8th*, 1948.]

65. *Some New Organo-selenium Compounds.*

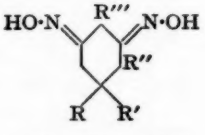
By F. E. King and D. G. I. Felton.

A new series of stable, red or orange organo-selenium compounds has been prepared by the oxidation of *cyclo*hexane-1 : 3-dione dioximes (II*a*—II*f*), using selenium dioxide. On the basis of analytical and physical data, these are called, tentatively, 7-*nitroso*-$\Delta^{3:7}$-*dihydrobenz*-2 : 1 : 3-*oxaselenazoles* (III*a*—III*f*). Selenium dioxide does not oxidise 5-*phenyl*-2-*methyl*cyclo*hexane*-1 : 3-*dione dioxime* (II*g*). Five new octahydrophenoxaselenin-1 : 9-dione 10-oxides (I*a*, I*b*, I*d*, I*e*, I*g*) (cf. Stamm and Gossrau, *Ber.*, 1933, **66**, 1558; Borsche and Hartmann, *ibid.*, 1940, **73**, 839) have also been prepared.

It has been noted (Waitkins and Clark, *Chem. Reviews*, 1945, **36**, 235) that selenium dioxide oxidations often appear to proceed *via* the formation of unstable intermediate organo-selenium compounds and that normally they decompose largely into the oxidation product, selenium, and water. Cases are known, however, in which the greater proportion of the product consists of a stable organo-selenium compound and the above authors provide an exhaustive table of these cases. It is relevant to note, in particular, the reactions between aromatic *o*-diamines and selenium dioxide, whereby an interesting series of compounds known as the piaselenoles are obtained (Hinsberg, *Ber.*, 1889, **22**, 863, 866, 2897; 1890, **23**, 1393; 1891, **24**, 5. For a full list of references, see Waitkins and Clark, *loc. cit.*), and the analogous reaction between 4 : 5-diamino-2 : 6-dihydroxy-1 : 3-dimethylpyrimidine and selenium dioxide (Sachs and Meyerheim, *Ber.*, 1908, **41**, 3957) giving 2 : 6-dihydroxy-1 : 3-dimethylpiaselenopurine. The oxidation of 5 : 5-dimethyl*cyclo*hexane-1 : 3-dione (" Dimedone ") by selenium dioxide, which yields the



(I*a*, R = R′ = R″ = R‴ = H; I*b*, R = Me, R′ = R″ = R‴ = H; I*c*, R = R′ = Me, R″ = R‴ = H; I*d*, R = Ph, R′ = R″ = R‴ = H; I*e*, R = R″ = Ph, R′ = R‴ = H; I*f*, R = R‴ = Ph, R′ = R″ = H; I*g*, R = R′ = Me, R″ = Ph, R‴ = H; I*h*, R = R′ = Me, R‴ = Ph, R″ = H.)



(II*a*, R = R′ = R″ = R‴ = H; II*b*, R = Me, R′ = R″ = R‴ = H; II*c*, R = R′ = Me, R″ = R‴ = H; II*d*, R = Ph, R′ = R″ = R‴ = H; II*e*, R = R″ = Ph, R′ = R‴ = H; II*f*, R = R′ = Me, R″ = Ph, R‴ = H; II*g*, R = Ph, R‴ = Me, R′ = R″ = H.)

organo-selenium compound (I*c*) (Stamm and Gossrau, *loc. cit.*; Borsche and Hartmann, *loc. cit.*) is again a closely similar reaction.

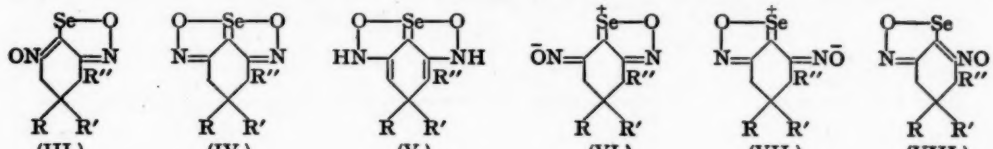
In the present work it was found that on attempted oxidation of *cyclo*hexane-1 : 3-dione dioxime (II*a*; Merling, *Annalen*, 1894, **278**, 28) by means of selenium dioxide, a very vigorous reaction occurred on heating the components in methanol or acetic anhydride, yielding in each case the same *product* as beautiful, long, red needles, containing selenium. Analysis indicated the empirical formula $C_6H_6O_2N_2Se$, and a micro-Rast molecular-weight determination confirmed this as the molecular formula. The reaction has been shown to be general for *cyclo*hexane-1 : 3-dione dioximes by the preparation of similar compounds starting from the following *cyclo*hexane-1 : 3-dione dioximes : 5-methyl (II*b*; Vorländer and Kalkow, *Ber.*, 1897, **30**, 1802), 5 : 5-dimethyl- (II*c*; Gittel, *Chem. Zentr.*, 1906 I, 34), 5-phenyl- (II*d*; Vorländer, *Ber.*, 1894, **27**, 2057), 4 : 5-*diphenyl*- (II*e*), and 4-*phenyl*-5 : 5-*dimethyl*- (II*f*). In all cases the products were highly crystalline red or orange-red compounds, the analyses of which agreed with the general formula $C_6H_3O_2N_2SeRR'R''$.

In sharp contrast, it was found that no such reaction occurred with a compound in which the 2-position in the dioxime was blocked; *e.g.*, 5-*phenyl*-2-*methyl*cyclo*hexane*-1 : 3-*dione dioxime* (II*g*) was recovered unchanged.

In general, the reaction appears to be stoicheiometrically: $C_6H_7O_2N_2RR'R'' + SeO_2 = C_6H_3O_2N_2SeRR'R'' + 2H_2O$, suggesting a dehydrogenation process coupled with incorporation of selenium. Dehydrogenation by selenium dioxide has been noted previously, acetonylacetone giving 1 : 2-diacetylethylene (Armstrong and Robinson, *J.*, 1934, 1650), and ethyl succinate giving the fumarate (Astin, Riley, and Newman, *J.*, 1933, 391), in each case hydrogen atoms being removed from activated methylene groups. In view of the failure of (II*g*) to react with selenium dioxide, where the active methylene group is blocked by substitution, a similar type of reaction appears applicable.

It might be expected that the closest analogy would be provided by the selenium dioxide oxidation of a *cyclo*hexane-1 : 3-dione. As noted above, this has been studied only in the case of 5 : 5-dimethyl*cyclo*hexane-1 : 3-dione, 3 : 3 : 7 : 7-tetramethyl-1 : 2 : 3 : 4 : 6 : 7 : 8 : 9-octahydrophenoxaselenin-1 : 9-dione 10-oxide (anhydromethone selenium oxide) (I*c*) being formed. The generality of the latter reaction has now been shown by the preparation of five more *compounds* of this series, *viz.*, (I*a*), (I*b*), (I*d*), and 2 : 3 : 7 : 8(or 3 : 4 : 6 : 7)-*tetraphenyl*-(I*e* or I*f*) and 2 : 8(or 4 : 6)-*diphenyl*-3 : 3 : 7 : 7-*tetramethyl*-1 : 2 : 3 : 4 : 6 : 7 : 8 : 9-*octahydrophenoxaselenin*-1 : 9-*dione* 10-*oxide* (I*g* or I*h*). These compounds are all golden-yellow and closely resemble that already described (I*c*) in their instability to light and dilute acids, selenium being rapidly deposited. This instability is undoubtedly due to the presence of a double enol ether linkage.

In the formation of these octahydrophenoxaselenin oxide derivatives, dehydrogenation at the reactive methylene group has been accompanied by a union of 2 molecules through the selenium atom. Once again, the presence of a methyl group at position 2 in the diketone molecule interferes with the normal course of oxidation and an attempt to oxidise 5-phenyl-2-methyl*cyclo*hexane-1 : 3-dione led to extensive decomposition. Except, however, for this similarity in the blocking behaviour of a 2-methyl group, the analogy between the oxidation of



(III.) (IV.) (V.) (VI.) (VII.) (VIII.)

(*a*, R = R′ = R″ = H; *b*, R = Me, R′ = R″ = H; *c*, R = R′ = Me, R″ = H; *d*, R = Ph, R′ = R″ = H; *e*, R = R″ = Ph, R′ = H; *f*, R = R′ = Me, R″ = Ph.)

the diketones and the dioximes cannot be drawn. It may be seen from the analytical data that no union of molecules occurs, and the products arise solely from an intramolecular dehydrogenation process. Further, the properties of the two classes of compound are very different. The red compounds obtained from the dioximes are very stable towards acids and light. They may be crystallised unchanged from a large volume of concentrated hydrochloric acid, without any deposition of selenium. (This behaviour shows that the nitrogen atoms are either not basic, or only extremely weakly so.) They decompose, with deposition of selenium, however, on warming with sodium hydroxide solution.

The isolation of products containing *gem*-dimethyl groups, *e.g.*, by the oxidation of (II*c*) or (II*f*), indicates that aromatisation of the nucleus has not occurred, and this limits the possible formulæ to (III), (IV), and (V).

Of these formulæ, (V) appears to be excluded by the fact that a Zerewitinoff determination of active hydrogen showed there was none present, while (IV) and (V) scarcely seem feasible on strain considerations. An objection to structure (III) is that the colour is not suggestive of a nitroso-compound, nor could it be induced to react with aniline in glacial acetic acid solution to form an azo-compound.

A preliminary polarographic study was made of (III*a*), obtained from *cyclo*hexane-1 : 3-dione dioxime (see Fig. 1). In phosphate buffer (pH 7·27), a polarographic wave was detected at a half-wave potential of −0·56 volt, with indications of a second wave at −1·64 volts (curve 3). The polarogram was not clear-cut, however, possibly owing to the disturbing influences of selenium on the dropping-mercury electrode. Under other conditions, *e.g.*, in M/20-sodium hydroxide, large erratic maxima were observed doubtless owing to decomposition in the presence of alkali (for explanations of these phenomena, see Kolthoff and Lingane, " Polarography ", Interscience, New York, pp. 113—140). As a comparison, polarograms of *p*-benzoquinone and *p*-nitrosodimethylaniline were made under the same conditions. The quinone, selected because of a formal resemblance to (V), gave a sharp wave at −0·21 volt (curve 2), while the nitroso-compound was reduced at a half-wave potential of −0·59 volt (curve 1). Although it must be emphasised that these results were of a semiquantitative nature only, it is perhaps of significance that the reduction potentials of the nitroso-compound and the organo-selenium compound are so close. Undoubtedly, structure (III) can be considerably modified by resonance between structures (VI), (VII), and (VIII), which could contribute to the stability of this series of compounds.

An examination of the ultra-violet absorption spectra of the compounds obtained from (II*a*) and (II*c*) showed that they were very closely related (see Fig. 2). The former (III*a*) gave maxima at 2270 (9910), 3000 (1450), and 3900 A. (4750), while the latter (III*c*) gave maxima

at 2250 (9840), 3000 (1385), and 3900 A. (4650), the figures in parentheses being the values of the molar extinction coefficient ($\varepsilon^{max.}_{molar}$). The interpretation of these spectra is complicated by the fact that selenium, when present in an organic molecule, exerts a pronounced bathochromic and hyperchromic effect (Brode, " Chemical Spectroscopy ", Wiley, New York, 1943, p. 260; cf. Behaghel and Schneider, *Ber.*, 1936, **69**, 88; Fisher and Hamer, *Proc. Roy. Soc.*, 1936, **154**, *A*, 703), and no useful deductions have been drawn from these results.

FIG. 1.

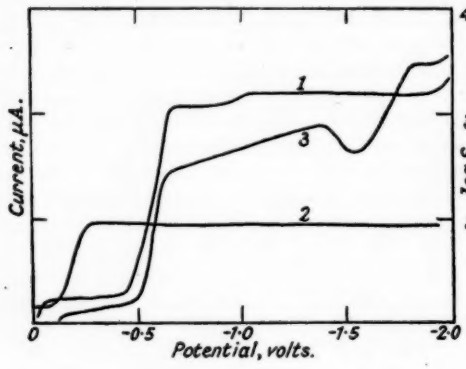
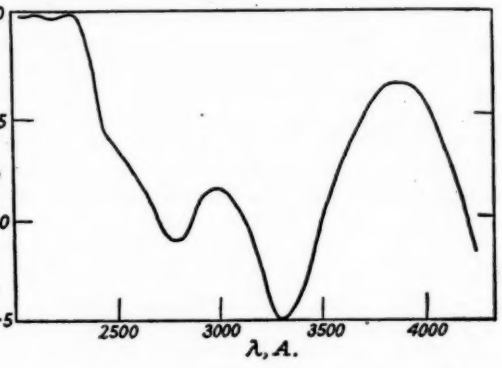


FIG. 2.



In a further attempt to elicit information as to the structure of this series of compounds, the dipole moment of (III*a*) was kindly determined by Mr. R. A. W. Hill at Oxford, who found the value of 2·90 ± 0·03 D. Since, however, the highly polar resonance forms (VI) and (VII) are equally probable and their moments nearly opposed, all the possible formulations could well have a moment of about 3·0 D. Accordingly, it is proposed, tentatively, to name these compounds as derivatives of 7-nitroso-$\Delta^{3:7}$-dihydrobenz-2 : 1 : 3-oxaselenazole (III*a*).

It is intended to continue the study of these interesting compounds.

EXPERIMENTAL.

(All m. p.s are uncorrected.)

7-Nitroso-$\Delta^{3:7}$-dihydrobenz-2 : 1 : 3-oxaselenazole (III*a*).—(i) *cyclo*Hexane-1 : 3-dione [prepared by catalytic reduction of resorcinol in alkaline solution (Hofmann-La Roche; B.P. 416,892; *Chem. Zentr.*, 1935, I, 632; Felton and King, *J.*, 1948, 1371)] was converted into the dioxime (II*a*) (Merling, *loc. cit.*). This substance (7·6 g., 1 mol.) in boiling methanol (50 ml.) was treated with finely powdered selenium dioxide (5·9 g., 1 mol.). A very vigorous reaction ensued, the solution becoming dark red but remaining clear. On cooling, long red needles (5·7 g., 49%) separated, which after recrystallisation from methanol melted at 106° [Found: C, 33·2; H, 2·94; N, 12·8; *M* (Rast), 207; active H (Zerewitinoff), 0. $C_8H_6O_2N_2Se$ requires C, 33·2; H, 2·77; N, 12·9%; *M*, 217]. Light absorption (methanol): $\lambda_{max.}$ 2270, 3000, 3900 A.; $\varepsilon_{max.}$ 9910, 1450, 4750.

(ii) The action of selenium dioxide in acetic anhydride on (II*a*) produced the same red *product*, m. p. 106°, undepressed on admixture with the previous specimen.

7-Nitroso-5-methyl-$\Delta^{3:7}$-dihydrobenz-2 : 1 : 3-oxaselenazole (III*b*).—5-Methyl*cyclo*hexane-1 : 3-dione dioxime (II*b*) (5·9 g.; Vorländer and Kalkow, *loc. cit.*) in boiling methanol (50 ml.) was treated with selenium dioxide (4·65 g., 1 mol.), and on cooling and adding water, the *product* separated as deep orange-red scales (5·4 g., 61%), which after one recrystallisation from aqueous methanol, melted at 91° (Found: C, 36·7; H, 3·47. $C_7H_8O_2N_2Se$ requires C, 36·4; H, 3·46%).

7-Nitroso-5 : 5-dimethyl-$\Delta^{3:7}$-dihydrobenz-2 : 1 : 3-oxaselenazole (III*c*).—(i) 5 : 5-Dimethyl*cyclo*hexane-1 : 3-dione dioxime (II*c*; 2·3 g., from dimedone; Gittel, *loc. cit.*) in boiling methanol (20 ml.) was oxidised with selenium dioxide (1·0 g., 1 mol.). The *product*, precipitated by addition of water, formed long, red needles (2·1 g., 52%), m. p. 109° from aqueous methanol [Found: C, 39·1; H, 4·26; N, 11·7; *M* (Rast), 205. $C_9H_{10}O_2N_2Se$ requires C, 39·2; H, 4·08; N, 11·4%; *M*, 245]. Light absorption (methanol): $\lambda_{max.}$ 2250, 3000, 3900 A.; $\varepsilon_{max.}$ 9840, 1385, 4650.

(ii) A repetition of this experiment using selenium dioxide (2 mols.) gave the same product, m. p. and mixed m. p. 109°, in 58% yield.

7-Nitroso-5-phenyl-$\Delta^{3:7}$-dihydrobenz-2 : 1 : 3-oxaselenazole (III*d*).—5-Phenyl*cyclo*hexane-1 : 3-dione dioxime (II*d*; 1·1 g.; Vorländer, *loc. cit.*) was oxidised in boiling ethanol (15 ml.) with selenium dioxide (0·55 g., 1 mol.). The red crystalline *oxaselenazole* was collected, and on crystallisation from aqueous methanol, formed fine, red needles (1·0 g., 67·5%), m. p. 165° (Found: C, 49·4; H, 3·61. $C_{13}H_{12}O_2N_2Se$ requires C, 49·2; H, 3·41%).

*4 : 5-Diphenyl*cyclo*hexane-1 : 3-dione Dioxime* (II*e*).—4 : 5-Diphenyl*cyclo*hexane-1 : 3-dione (1·4 g.; Borsche, *Ber.*, 1909, **42**, 4498) was converted in the usual manner into the *dioxime*, which crystallised from aqueous ethanol as colourless bunches of needles, m. p. 150° (decomp.) (Found: C, 71·4; H, 5·99.

$C_{15}H_{12}O_2N_2,\frac{1}{2}H_2O$ requires C, 71·3; H, 6·27%. Found, on a sample dried at 120° in a high vacuum: C, 72·2; H, 6·14. $C_{15}H_{12}O_2N_2,\frac{1}{4}H_2O$ requires C, 72·4; H, 6·20%. Further attempts to dehydrate the sample led to decomposition).

7-Nitroso-4 : 5-diphenyl-$\Delta^{3:7}$*-dihydrobenz-2 : 1 : 3-oxaselenazole* (III*e*).—4 : 5-Diphenyl*cyclo*hexane-1 : 3-dione dioxime (II*e*, 0·7 g.) was oxidised in boiling methanol (7 ml.) with selenium dioxide (0·26 g., 1 mol.), and the *product*, collected after careful precipitation with water, crystallised from aqueous methanol as small, red needles (0·55 g., 63%), m. p. 180—181° (Found: C, 58·1; H, 3·61. $C_{15}H_{14}O_2N_2Se$ requires C, 58·5; H, 3·79%).

*4-Phenyl-5 : 5-dimethyl*cyclo*hexane-1 : 3-dione Dioxime* (II*f*).—4-Phenyl-5 : 5-dimethyl*cyclo*hexane-1 : 3-dione (3·0 g.; Borsche, *loc. cit.*) was treated for 3 hours under reflux with an ethanolic solution of hydroxylamine (from the hydrochloride, 1·8 g.). The solution was then concentrated to about 10 ml., and water cautiously added until crystallisation commenced. The *dioxime* (2·2 g., 64·5%) was collected and, after several crystallisations from aqueous ethanol, formed rosettes of colourless prisms, m. p. 119—120° (Found: C, 63·5; H, 7·12. $C_{14}H_{18}O_2N_2,H_2O$ requires C, 63·6; H, 7·58%. Found, on a sample dried at 100° in a high vacuum: C, 66·7; H, 7·47. $C_{14}H_{14}O_2N_2,\frac{1}{4}H_2O$ requires C, 67·1; H, 7·39%).

7-Nitroso-4-phenyl-5 : 5-dimethyl-$\Delta^{3:7}$*-dihydrobenz-2 : 1 : 3-oxaselenazole* (III*f*).—4-Phenyl-5 : 5-dimethyl*cyclo*hexane-1 : 3-dione dioxime (II*f*, 2·0 g.) was oxidised in boiling methanol (25 ml.) with selenium dioxide (0·9 g., 1 mol.), and the *product*, precipitated by the addition of water, crystallised from aqueous methanol, forming red rhombs, m. p. 137° (Found: C, 52·7; H, 4·66. $C_{14}H_{14}O_2N_2Se$ requires C, 52·3; H, 4·36%).

*5-Phenyl-2-methyl*cyclo*hexane-1 : 3-dione Dioxime* (II*g*).—5-Phenyl-2-methyl*cyclo*hexane-1 : 3-dione (1·1 g.; Mattar, Hastings, and Walker, *J.*, 1930, 2455) was treated with an ethanolic solution of hydroxylamine (from the hydrochloride, 1·08 g., 2 mols.). The mixture, after refluxing on the water-bath for 2 hours, was evaporated to small volume, and water added until crystallisation was initiated. The *dioxime* (0·8 g., 63%) formed colourless needles from aqueous ethanol, m. p. 188° (efferv.) (Found: C, 67·7; H, 6·94. $C_{13}H_{16}O_2N_2$ requires C, 67·2; H, 6·90%). Attempted oxidation of this dioxime by means of selenium dioxide in boiling methanol, under the conditions described above, was unsuccessful, some decomposition being observed. The bulk (approx. 85%) of the dioxime was recovered unchanged, m. p. 188° (efferv.) undepressed on admixture with an authentic specimen.

1 : 2 : 3 : 4 : 6 : 7 : 8 : 9-Octahydrophenoxaselenin-1 : 9-dione 10-Oxide (I*a*).—*cyclo*Hexane-1 : 3-dione (6·0 g.) in hot methanol (20 ml.) was oxidised with selenium dioxide (3·75 g., 1 mol.); a vigorous reaction ensued, giving a dark yellow solution from which, on cooling, golden-yellow, shining crystals (6·2 g., 77·5%) were obtained. On recrystallisation from methanol, *1 : 2 : 3 : 4 : 6 : 7 : 8 : 9-octahydrophenoxaselenin-1 : 9-dione 10-oxide* formed golden-yellow needles, m. p. 180° (decomp.) (Found: C, 48·3; H, 4·2. $C_{12}H_{12}O_4Se$ requires C, 48·1; H, 4·0%). This substance decomposes on prolonged exposure to daylight, or on warming with dilute mineral acid, with deposition of selenium as a red powder.

3 : 7-Dimethyl-1 : 2 : 3 : 4 : 6 : 7 : 8 : 9-octahydrophenoxaselenin-1 : 9-dione 10-Oxide (I*b*).—5-Methyl*cyclo*hexane-1 : 3-dione (1·3 g.) in hot methanol (20 ml.) was oxidised by selenium dioxide (1·2 g.), and on cooling the *oxide* crystallised. After recrystallisation from ethyl acetate, it formed glittering, golden scales, m. p. 185° (decomp.), containing solvent of crystallisation (Found: C, 51·9, 52·0; H, 5·49, 5·45. $C_{14}H_{16}O_4Se,\frac{1}{2}C_4H_8O_2$ requires C, 51·8; H, 5·40%). Attempted removal of the solvent led to decomposition.

3 : 7-Diphenyl-1 : 2 : 3 : 4 : 6 : 7 : 8 : 9-octahydrophenoxaselenin-1 : 9-dione 10-Oxide (I*d*).—5-Phenyl-*cyclo*hexane-1 : 3-dione (1·0 g.) was oxidised in the usual manner with selenium dioxide (0·6 g., 1 mol.) in hot methanol. Recrystallised from benzene–ethanol, the *oxide* formed glittering, golden plates, m. p. 187—188° (with reddening, Se?) (Found: C, 64·0; H, 4·64. $C_{24}H_{20}O_4Se$ requires C, 63·9; H, 4·43%).

2 : 3 : 7 : 8 (*or* *3 : 4 : 6 : 7*)*-Tetraphenyl-1 : 2 : 3 : 4 : 6 : 7 : 8 : 9-octahydrophenoxaselenin-1 : 9-dione 10-Oxide* (I*e* or I*f*).—4 : 5-Diphenyl*cyclo*hexane-1 : 3-dione (0·8 g.) was oxidised in methanol by selenium dioxide (0·34 g., 1 mol.). The *product*, precipitated on addition of a little water, formed very small pale yellow needles, m. p. 164° (decomp.), on crystallisation from aqueous methanol (Found: C, 67·9; H, 5·02. $C_{36}H_{28}O_4Se,2H_2O$ requires C, 67·6; H, 5·01%). Attempts to dehydrate the sample led to decomposition with liberation of selenium.

2 : 8 (*or* *4 : 6*)*-Diphenyl-3 : 3 : 7 : 7-tetramethyl-1 : 2 : 3 : 4 : 6 : 7 : 8 : 9-octahydrophenoxaselenin-1 : 9-dione 10-Oxide* (I*g* or I*h*).—4-Phenyl-5 : 5-dimethyl*cyclo*hexane-1 : 3-dione (1·0 g.) in hot methanol was oxidised as above with selenium dioxide (0·37 g.), and the *product* precipitated by dropwise addition of water. It crystallised from aqueous methanol as microscopic, primrose-yellow needles, m. p. 133° (Found: C, 66·6; H, 5·81. $C_{28}H_{28}O_4Se$ requires C, 66·3; H, 5·52%).

The award of a Medical Research Council Studentship and of an I.C.I. Fellowship (to D. G. I. F.) is gratefully acknowledged. The authors thank Mr. G. Meacock for assistance with the polarograms, Mr. R. A. W. Hill for his determination of the dipole moment, and Dr. F. B. Strauss, who determined the ultra-violet absorption spectra. One of them (D. G. I. F.) is indebted to Professor G. R. Clemo for facilities at King's College (University of Durham).

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[*Received, May 11th*, 1948.]

66. *Reactions of Ethylene Oxides. Part II. Reactions with Thioamides, Thiols, and Inorganic Sulphur Salts.*

By C. C. J. Culvenor, W. Davies, and N. S. Heath.

Alkali thioalkoxides react with extreme ease with ethylene oxides to form the 2-hydroxyalkyl sulphides, and alkali sulphides react in a similar manner. With a simple ethylene oxide, potassium *o*-aminothiophenoxide gives a dihydrobenz-1 : 4-thiazine, and with a glycidic ester forms a 3-ketodihydrobenz-1 : 4-thiazine substituted in the 2-position, and this compound is readily hydrolysed to the 3-ketodihydrobenzthiazine. Ethylene oxide reacts with thiosulphates as well as with neutral sulphites to form an isethionate. Some simple ethylene oxides are converted into the corresponding sulphides not only by thiourea but by a number of compounds containing the S:C·NH_2 or HS·C:NH groups, such as xanthamide, thioacetamide, and thiobarbituric acid. Thiourea with stilbene oxide yields stilbene and sulphur and no stilbene sulphide, and this type of reaction, sometimes accompanied by the formation of thiazolidine compounds, can occur with ethylene oxides containing an acyl group.

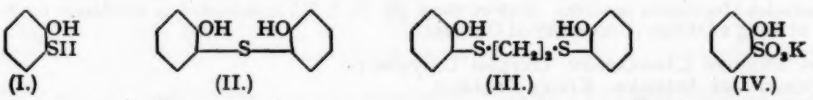
This paper describes the continuation and extension of the work of Culvenor, Davies, and Pausacker (*J.*, 1946, 1050) on the reactions of some simple ethylene oxide types with thiourea, xanthates, and related compounds. It has now been found that *cyclo*hexene oxide or epichlorohydrin reacts not only with thiourea and thiocarbanilide but also with xanthamide, thioacetamide, thiobenzamide, and thiobarbituric acid to form the ethylene sulphide and the oxygen analogue of the thio-compound used.

Thiourea with butadiene monoxide and 4-methyl*cyclo*hexene oxide gives the expected sulphides, but stilbene oxide yields only stilbene, sulphur, and urea, no cyclic compound being detected. Apparently, unlike the stable tetraphenylethylene sulphide (Schönberg and Barak, *J.*, 1939, 1074), stilbene sulphide is unstable. The presence of strongly polar groups in ethylene oxides hinders the formation of ethylene sulphides when thiourea in alcoholic or aqueous-alcoholic solution is used. Benzylideneacetone oxide (4-phenyl-3 : 4-epoxybutan-2-one) gives a yellow amorphous solid containing nitrogen and sulphur. Bodforss (*Ber.*, 1918, **51**, 212) found that 1-benzoyl-2-*m*-nitrophenylethylene oxide gave a nitrothiazolidine, m. p. 176°, but a repetition of his work shows that only a small amount of this is formed, most of the pure product obtained being *m*-nitrobenzylideneacetophenone. This, and selenium, are the products from 1-benzoyl-2-*m*-nitrophenylethylene oxide and potassium selenocyanate, and similarly stilbene oxide yields stilbene and selenium only.

The condensation of alcoholic thiourea with ethyl dimethylglycidate produces a thiazolidine derivative, m. p. 285°, which is being investigated, while with ethyl phenylglycidate at ordinary temperatures the products are ethyl cinnamate, sulphur, and urea. Xanthamide, thioacetamide, and thiobenzamide also give ethyl cinnamate and sulphur.

Ethylene oxides are most reactive towards solutions of alkali hydrogen sulphides and alkali derivatives of thiols. Thus *cyclo*hexene oxide and potassium hydrogen sulphide in the cold give 2-*mercapto*cyclo*hexanol* (I) and bis-2-hydroxy*cyclo*hexyl sulphide (II) in almost equal amounts. Contrary to the assumption of Mousseron (*Compt. rend.*, 1943, **216**, 812), who obtained only bis-2-hydroxy*cyclo*hexyl sulphide (II) from sodium sulphide and *cyclo*hexene oxide, the thiol (I) is quite stable and does not condense spontaneously to (II); (II) is produced by further reaction of the potassium salt of (I) with another oxide molecule.

Alkali derivatives of thiols react with ethylene oxide at 0° to give almost quantitative yields of the R·S·CH_2·CH_2·OH derivative. This change has been effected with potassium thioethoxide, thio-*n*-butoxide, and thio*iso*amyloxide on ethylene oxide. Similarly, the dipotassium salt of ethylenedithiol and *cyclo*hexene oxide give 1 : 2-*bis*-(2-*hydroxy*cyclo*hexylthio*)-*ethane* (III).

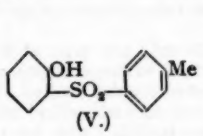


(I.) (II.) (III.) (IV.)

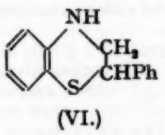
Aqueous sodium sulphite rapidly reacts with ethylene oxide to form sodium hydroxide and sodium isethionate, CH_2(OH)·CH_2·SO_3Na. Potassium isethionate is produced by the interaction of potassium thiosulphate and ethylene oxide. In this case, the first product may be CH_2(OH)·CH_2·S·SO_3K which the potassium hydroxide formed would be expected to hydrolyse to potassium sulphite (which then reacts with ethylene oxide to form potassium isethionate) and the sulphenic acid, CH_2(OH)·CH_2·S·OH. This mechanism is supported by the detection

in the reaction mixture of a sulphinic acid, into which a sulphenic acid is readily converted (Fromm and Erfurt, *Ber.*, 1909, **42**, 3816). Similarly, *cyclo*hexene oxide and potassium thiosulphate forms the *hydroxy-sulphonate* (IV).

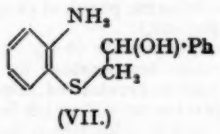
This ready opening of the ethylene oxide ring by sulphites and thiosulphates seems to be brought about, as in the case of sulphides and thioalkoxides, by the presence of a negatively charged sulphur atom. Thus aqueous sodium sulphate is without action. It is noteworthy that sodium selenite also does not react, and this may be due to the charge on the selenite ion not residing on the selenium atom, which is also indicated by the inertness of sodium selenite towards iodine.



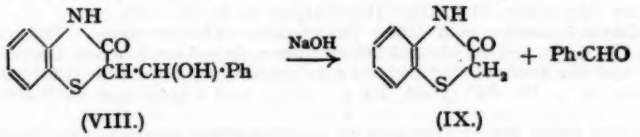
(V.)



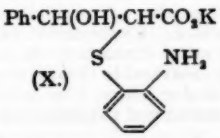
(VI.)



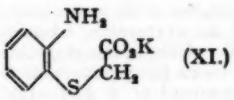
(VII.)



(VIII.) (IX.)



(X.)



(XI.)

Reaction of Oxides with o-*Aminothiophenol.*—This reaction takes place readily with one molecule of alcoholic alkali. Ethylene oxide condenses to form dihydrobenzthiazine, identified by its phenyl *iso*thiocyanate derivative (" Beilstein," Vol. 27, p. 34).

*cyclo*Hexene oxide forms *hexahydrophenthiazine*, and styrene oxide forms 2-*phenyldihydrobenzthiazine* (VI). This structure has been proved by the synthesis of (VI) from *o*-aminothiophenol and 2-iodo-2-phenylethanol, whereas *o*-aminothiophenol and 2-bromo-1-phenylethanol give o-*aminophenyl* 2-*hydroxy*-2-*phenylethyl sulphide* (VII). The attachment of the S-group to the α-carbon atom of styrene oxide is to be expected from the reactions of styrene oxide outlined by Emerson (*J. Amer. Chem. Soc.*, 1945, **67**, 516).

Benzoylphenylethylene oxide and *o*-aminothiophenol give one of the two possible *benzoylphenyldihydrobenzthiazines*, but no pure product is obtained from benzylideneacetone oxide.

With glycidic esters, $R_1R_2C\!\!<\!\!\overset{O}{}\!\!>\!\!CH{\cdot}CO_2Et$, the ring closure occurs on the ester group in preference to the hydroxyl group, and if the ester group is hydrolysed before this can take place (hydrolysis of a glycidic ester is extremely rapid) ring closure does not occur at all. Thus ethyl phenylglycidate produces a mixture of 3-*keto*-2-(α-*hydroxybenzyl*)*dihydrobenzthiazine* (VIII) and *potassium* β-*hydroxy*-α-(o-*aminophenylthio*)-β-*phenylpropionate* (X), together with the well-known 3-ketodihydrobenzthiazine (IX), into which (VIII) is readily converted by being warmed with dilute alkali. From ethyl dimethylglycidate, only (IX) and the corresponding *o*-aminophenylthioacetate (XI) are obtained, the unstable intermediate spontaneously splitting off acetone, the presence of which in the reaction mixture can be shown. Both (X) and (XI) are rapidly converted into the cyclic amides (VIII) and (IX) respectively on acidification. The yields of products from the glycidic ester reactions are greatly reduced by the various hydrolytic transformations to which these compounds are subject in alkaline media. This is particularly marked with ethyl phenylglycidate.

Experimental.

Butadiene Sulphide.—Thiourea (10 g., 1·1 mols.) in methyl alcohol (100 ml.) when stirred with butadiene monoxide (10 g., 1·0 mol.) for 4 hours at 20° yields, when the mixture is poured into water and extracted with ether, *butadiene sulphide* (6·0 g., 50%), b. p. 103—104°. This gradually polymerises even in a sealed tube (Found : S, 37·5. C_4H_6S requires S, 37·2%).

4-*Methyl*cyclo*hexene Sulphide.*—4-Methyl*cyclo*hexene oxide (5 g.) on being stirred with thiourea (5 g.) in methyl alcohol (20 ml.) for 1 hour at 60°, poured into water (150 ml.), and extracted with chloroform, gives a 60% yield of 4-*methyl*cyclo*hexene sulphide*, b. p. 85—86°/25 mm., $n_D^{25°}$ 1·5097 (Found : S, 24·9. $C_7H_{12}S$ requires S, 25·0%).

Reaction of Thiourea with Other Ethylene Oxides.—Thiourea (1·0 g.) in alcohol (20 ml.) reacts with

stilbene oxide (2·0 g.) for 6 days at 35° to produce sulphur (0·2 g., 65%) and stilbene (1·55 g., 80%), the latter being separated by solution in acetone, which also extracts a little unchanged oxide, m. p. 65°. The same reaction proceeds slowly at room temperature. If less than the theoretical amount of thiourea is used, pure urea is obtained by evaporation of the aqueous filtrate.

1-Benzoyl-2-*m*-nitrophenylethylene oxide (1 g.) and thiourea (2·5 g.) are heated with shaking in alcohol (20 ml.) till dissolved, and refluxed for a further 3 minutes before being cooled and freed from alcohol under reduced pressure. The residue, washed with water and recrystallised from alcohol, gives a small amount of white crystals of *m*-nitrobenzylideneacetophenone, m. p. 144°, identified by mixed melting point with an authentic specimen prepared from 1-benzoyl-2-*m*-nitrophenylethylene oxide and potassium iodide. The main product (from mother liquors) is amorphous and complex, but repeated recrystallisation from alcohol gives a very small quantity of a crystalline, yellow powder, m. p. 175°, which shows the same physical properties and colour reaction as the thiazolidine, m. p. 176°, obtained by Bodforss (*loc. cit.*).

Ethyl phenylglycidate (6·4 g.) and thiourea (2·5 g.) in alcohol (20 ml.) are kept at 30° for 16 hours and then at room temperature for 2 days. Filtration gives a mixture of large white crystals of urea (1·1 g.), and yellow crystals of sulphur (0·6 g.), which can be separated mechanically. Dilution of the filtrate precipitates an oil which is extracted with ether and distilled to yield ethyl cinnamate, b. p. 178°/65 mm. (4·0 g.), identified by hydrolysis to cinnamic acid, m. p. 135°, and by the addition of bromine to form the dibromide, Ph·CHBr·CHBr·CO_2Et, m. p. 74—75°.

Reactions of Ethylene Oxides with Other Thioamides.—Thioacetamide. Thioacetamide (5 g.) and *cyclo*hexene oxide (6·5 g.) in methyl alcohol (30 ml.) are refluxed for 5 hours, the solvent removed under reduced pressure, and the product distilled, to give acetamide, b. p. 120—132°/20 mm., solidifying to hygroscopic crystals, m. p. 73—76° (yield, 3·4 g.; 85%), and a large non-distillable sulphur-containing residue.

Thioacetamide and ethyl phenylglycidate in equimolecular amounts are dissolved in alcohol and refluxed for 2 hours or kept at room temperature for 3 weeks. A precipitate of sulphur is removed, and the filtrate diluted with water and extracted with ether. Evaporation of the aqueous layer yields some unchanged thioacetamide, while the extract gives ethyl cinnamate, b. p. 154—159°/26 mm.

Thiobenzamide. Ethyl phenylglycidate (5 g.) and thiobenzamide (3·6 g.) in absolute alcohol (90 ml.), after 4 weeks at room temperature or 3 hours' heating under reflux, give sulphur (0·6 g.; 72%), benzamide (m. p. and mixed m. p. 128—129°), and a little unchanged thiobenzamide, m. p. 115°, and ethyl cinnamate.

Xanthamide. Xanthamide (5·7 g.) and epichlorohydrin (5·9 g.; 1·2 mols.) are refluxed for 1 hour in alcohol (20 ml.); the mixture is then diluted with water and extracted with ether, to give a small amount of chloropropylene sulphide, b. p. 60—85°/100 mm., and an 83% yield of urethane (4·0 g.), b. p. 91°/25 mm., 170—180°/760 mm., with a large non-distillable residue. The identity of the urethane was confirmed by formation of benzylidenediurethane, m. p. 178°, with benzaldehyde and hydrochloric acid. Xanthamide and ethyl phenylglycidate in alcohol give sulphur and ethyl cinnamate.

Thiobarbituric acid. Thiobarbituric acid (3·6 g.) and ethylene oxide (1·3 g.) in water (40 ml.) give, after a week at room temperature, a mixture of solid ethylene sulphide polymer and barbituric acid which is separated with hot water. The barbituric acid was identified by heating it with benzaldehyde to form 5-benzylidenebarbituric acid, m. p. 260°, which loses benzaldehyde again on being heated with dilute sodium hydroxide solution. Thiobarbituric acid gives sulphur and ethyl cinnamate by reaction with ethyl phenylglycidate as above.

Reaction of Alkali Thioalkoxides with Ethylene Oxides.—The additions to ethylene oxide are effected by adding the oxide (2·2 g.) with shaking and cooling to an ice-cold solution of a small excess of thiol in alcoholic potassium hydroxide [2·8 g. (1 mol.) in 30 ml. of 80% alcohol]. After standing overnight, the mixture is diluted with water, acidified with N-sulphuric acid, and extracted with chloroform. Ethylthiol (3·2 g.) gives ethyl 2-hydroxyethyl sulphide (4·8 g.; 91%), b. p. 81°/20 mm.; *n*-butylthiol (4·6 g.) gives 2-hydroxyethyl *n*-butyl sulphide (6·6 g.; 99%), b. p. 103°/16 mm., $n_D^{20°}$ 1·482; and *iso*amylthiol (5·3 g.) gives 2-hydroxyethyl *iso*amyl sulphide (7·3 g.; 99%), b. p. 113°/16 mm., $n_D^{20°}$ 1·475.

When *cyclo*hexene oxide (9·8 g.) is added to a potassium hydrogen sulphide solution prepared by saturating a solution of potassium hydroxide (5·6 g.) in alcohol (50 ml.) with hydrogen sulphide at 0°, the heat of reaction keeps the temperature at about 45° for ½ hour. After standing overnight, the mixture is worked up as above to yield 5·8 g. (44%) of 2-*mercapto*cyclo*hexanol* (I), b. p. 100°/18 mm., and 6·1 g. (53%) of bis-2-hydroxy*cyclo*hexyl sulphide (II), b. p. 148°/0·7 mm., which crystallises on standing, and then has m. p. 60—64° (impure). A small fraction is obtained at 92°/18 mm. and may be the geometrical isomer of (I). If the passage of hydrogen sulphide is continued while the reaction is proceeding, the yield of (I) rises to 70% while that of (II) falls to 29%. 2-Mercapto*cyclo*hexanol is a stable mobile oil and can be completely redistilled after being kept at room temperature for 7 days (Found: S, 23·9. $C_6H_{12}OS$ requires S, 24·24%). Treated with alcoholic potassium hydroxide and chloro-2:4-dinitrobenzene, it gives a bright yellow 2:4-*dinitrophenyl thioether*, m. p. 135° (Found: C, 48·3; H, 5·3. $C_{12}H_{14}O_5N_2S$ requires C, 48·3; H, 4·6%). On being warmed with 50% sulphuric acid, (I) is immediately converted into a solid white polymer with the odour of *cyclo*hexene sulphide (cf. Bennett, *J.*, 1922, **121**, 2144, who records similar behaviour with mercaptoethanol). Boiling with anhydrous magnesium sulphate does not appear to cause dehydration.

*cyclo*Hexene oxide (4·9 g.), added to a solution of potassium hydroxide (2·8 g.; 1 mol.) and ethylenedithiol (2·3 g.; 0·5 mol.) in alcohol (30 ml.), reacts with only small heat evolution; after 2 days in an incubator at 40°, the alcohol is removed under reduced pressure, water is added, and the resulting solution is extracted with chloroform, to give 1:2-*bis*-(2-*hydroxy*cyclo*hexylthio*)*ethane* (III), b. p. 132—136°/0·2 mm. (6·5 g.; 90%). Once purified, it solidifies and can be recrystallised from benzene–light petroleum (1:1) to form large prisms, m. p. 47—49°. It is very soluble in all organic solvents except light petroleum, and readily soluble in water (Found: S, 21·9. $C_{14}H_{28}O_2S_2$ requires S, 22·1%).

Reaction of Ethylene Oxides with Thiosulphates.—Alcohol is added to potassium thiosulphate (10 g.) in water (50 ml.) until a faint milkiness persists, and then excess of ethylene oxide (10 g.) is added

gradually with cooling. The solution rapidly becomes alkaline; after it has been left overnight and concentrated, potassium isethionate crystallises out in 60% yield (based on thiosulphate). On recrystallisation from aqueous alcohol, this melts at 192°; acetylation gives a product, m. p. 258°, agreeing with the observations of Lauer and Hill (*J. Amer. Chem. Soc.*, 1936, **58**, 1873), and it is identical with a sample obtained using potassium sulphite instead of thiosulphate. The aqueous mother liquor, after filtration from the isethionate and neutralisation, gives a strong permanent reddish-brown colouration with ferric chloride, indicating the presence of a sulphinate. A solution of potassium isethionate does not give this colour.

*cyclo*Hexene oxide (5 g.) is added to sodium thiosulphate (10 g.) in water (25 ml.), followed by sufficient alcohol to give solution. After 2 hours' refluxing, the mixture is evaporated to dryness and the sodium 2-hydroxy*cyclo*hexylsulphonate washed with ether and crystallised from aqueous alcohol. Yield, 5·0 g. (50%) (Found: C, 35·1; H, 5·5; S, 16·4; Na, 11·8. Calc. for $C_6H_{11}O_4SNa$: C, 35·6; H, 4·46; S, 15·8; Na, 11·4%*). Evaporation of the ether washings gives *cyclo*hexane-1 : 2-diol (0·3 g.), m. p. 103°.

*Reaction of Ethylene Oxides with Sodium Toluene-*p*-sulphinate.*—Ethylene oxide (20 g.) is added slowly with cooling to sodium toluene-*p*-sulphinate (18 g.) dissolved in aqueous alcohol, and the mixture is left overnight. Ether-extraction gives an oil, b. p. 195°/23 mm. (11 g.; 55%), which solidifies, and after crystallisation from acetone has m. p. 57°. Otto (*J. pr. Chem.*, 1884, **30**, 356) reports *p*-tolyl 2-hydroxyethyl sulphone, m. p. 54—55°, with similar solubilities.

*cyclo*Hexene oxide (9·5 g.) and sulphinate (18 g.) are refluxed in aqueous alcohol for 2 hours and poured into water. Extraction with ether gives o-*hydroxy*cyclo*hexyl* p-*tolyl sulphone* (V) (13 g.; 50%), which separates from alcohol–acetone in white needles, m. p. 123° (Found: C, 61·9; H, 7·9. $C_{13}H_{18}O_3$ requires C, 61·4; H, 7·1%).

Action of Potassium Selenocyanate on Oxides.—When potassium selenocyanate (1·4 g.) and stilbene oxide (1·9 g.) or 1-benzoyl-2-*m*-nitrophenylethylene oxide (2·7 g.) are refluxed in methyl alcohol (25 ml.) for 2 hours, selenium (0·7 g.; 90%) is deposited as a red powder. The alcohol solution is diluted with water and extracted with ether, the extract evaporated, and the residue crystallised from alcohol to give stilbene or *m*-nitrobenzylideneacetophenone according to the oxide used.

Reactions with o-*Aminothiophenol.*—The original method of preparation of *o*-aminothiophenol (reduction of *oo'*-dinitrodiphenyl disulphide with tin and hydrochloric acid) is found to be much inferior to that used by Sullivan and Hesse (*U.S. Public Health Reports*, 1929, **44**, 1599), *viz.*, the fusion of mercaptobenzthiazole with potassium hydroxide. By employing this method essentially but diluting the neutralised fusion mixture from mercaptobenzthiazole (170 g.) and potassium hydroxide (600 g.) with a little carbon tetrachloride and filtering to facilitate a normal extraction, an almost theoretical yield of *o*-aminothiophenol (125 g.) is obtained.

Simple ethylene oxides. The oxide (0·01 mol.) is added with shaking and cooling if necessary (*e.g.*, ethylene oxide causes great heat evolution) to a solution of *o*-aminothiophenol (1·25 g.) and potassium hydroxide (0·56 g.) in alcohol (10 ml.). The mixture is refluxed for ½ hour, then cooled and diluted with water to separate the product. From ethylene oxide is obtained dihydrobenzthiazine, b. p. 203—210°/20 mm., identified by formation of a derivative, m. p. 128—129°, with phenyl *iso*thiocyanate ("Beilstein," Vol. 27, p. 34). *cyclo*Hexene oxide (1 g.) gives *hexahydrophenthiazine* (2·2 g.; 99%), crystallising from aqueous alcohol or light petroleum in colourless needles, m. p. 81° (Found: S, 15·4; N, 6·82. $C_{12}H_{15}NS$ requires S, 15·6; N, 6·83%). Styrene oxide (1·2 g.) gives *2-phenyldihydrobenzthiazine* (VI), m. p. 103°, which solidifies only after dissolution in dilute hydrochloric acid, filtration of the solution, and reprecipitation with alkali. (VI) crystallises from aqueous alcohol and can be sublimed in a vacuum above its m. p. (Found: S, 14·0, 14·2; N, 6·08. $C_{14}H_{13}NS$ requires S, 14·1; N, 6·17%).

Styrene halohydrins. The two halohydrins required were prepared as follows: 2-iodo-2-phenylethanol by the action of hydriodic acid on styrene oxide (Tiffeneau and Fourneau, *Bull. Soc. chim.*, 1913, **13**, 975); 2-bromo-1-phenylethanol by shaking styrene with hot bromine water (Read and Reid, *J.*, 1928, 1488), and purifying the product by distillation.

A solution of 2-iodo-2-phenylethanol (2·5 g.) in alcohol (15 ml.) added to *o*-aminothiophenol (1·35 g.) and potassium hydroxide (0·56 g.) in alcohol (10 ml.) and refluxed for ½ hour before being cooled and diluted with water, gives an oil which after purification as above solidifies to a crystalline powder, m. p. 101°, identified by mixed m. p. with the product (VI) from styrene oxide. When 2-bromo-1-phenylethanol is treated in the same way, the product is an oil which gives a positive test for a primary aromatic amine (by diazotisation and coupling with β-naphthol). The extracted oil, on treatment with concentrated hydrochloric acid, is converted into a water-soluble hydrochloride which, although quite stable in the dry state, reddens considerably when heated in solution. The *hydrochloride* of (VII) is fairly soluble in alcohol, insoluble in ether and chloroform, and is purified for analysis by dissolution in cold absolute alcohol and precipitation with ether to form feathery needles, m. p. 172° (Found: C, 60·2; H, 5·6. $C_{14}H_{16}ONCl$S requires C, 59·8; H, 5·7%). The hydrochloride also gives the diazotisation test for a primary amine. Attempts at ring-closure by refluxing with acid or alkali yield only oily products.

Benzoylphenyldihydrobenzthiazine is obtained when benzoylphenylethylene oxide (1·1 g.) is kept for 2 days at room temperature with *o*-aminothiophenol (0·6 g.) and potassium hydroxide (0·3 g.) in alcohol (7 ml.). The thiazine separates from the dark red solution, and is crystallised from alcohol to form large yellow prisms, m. p. 187·5° (Found: S, 9·94; N, 4·26. $C_{21}H_{17}ONS$ requires S, 9·67; N, 4·23%).

Glycidic esters. Ethyl dimethylglycidate (14·4 g.) is kept for 24 hours at room temperature with *o*-aminothiophenol (12·5 g.) and potassium hydroxide (5·6 g.) in alcohol (75 ml.), then refluxed for 7 hours. Filtration of the pasty mass obtained gives a mixture of potassium *o*-aminophenylthioacetate (XI) (5·6 g.) and 3-ketodihydrobenzthiazine (IX) (0·9 g.) which are separated by crystallisation from alcohol. Dilution of the filtrate with water yields a further quantity (2·5 g.) of (IX) which crystallises from alcohol in long needles, m. p. 176°, which sublime readily at 140°/15 mm. (Found: C, 58·9;

H, 4·45; N, 8·70; S, 19·8. Calc. for C_8H_7ONS: C, 58·2; H, 4·2; N, 8·50; S, 19·4%). A mixture with 3-ketodihydrobenzthiazine prepared by the method of Hofmann (*Ber.*, 1880, **13**, 1234), by warming *o*-aminothiophenol with chloroacetic acid, gives no depression of the m. p. (IX) is insoluble in hydrochloric acid and cold sodium hydroxide solution but readily soluble in hot sodium hydroxide solution from which it crystallises unchanged if cooled quickly. On being boiled for a few minutes with concentrated potassium hydroxide solution, it is converted into a potassium salt identical with (XI), the second reaction product. This salt is readily soluble in hot alcohol from which it separates in large leafy crystals, m. p. 268° (Found: K, 17·76. Calc. for $C_8H_8O_2NSK$: K, 17·6%). The aqueous solution of (XI) gives no colour with sodium nitroprusside, but, when it is mixed with sodium nitrite and acidified with hydrochloric acid, the resultant solution forms a red dye with alkaline β-naphthol. When a solution of (XI) alone is acidified, the thiazine (IX) separates in a few minutes. The presence of acetone in the aqueous filtrate from the main reaction was demonstrated by means of the Wilbur modification of the Légal test (*Chemist-Analyst*, 1931, **20**, No. 4, 11; *Chem. Abs.*, 1931, **25**, 4202).

When ethyl phenylglycidate (4·8 g.) is added with shaking and cooling to *o*-aminothiophenol (5·1 g.) and potassium hydroxide (1·4 g.) in alcohol (20 ml.), the ester is hydrolysed immediately, and potassium phenylglycidate separates. This salt crystallises from alcohol to form silvery plates, m. p. 285° (decomp.) (Found: K, 19·8. Calc. for $C_9H_7O_3K$: K, 19·6%). Acidification of an aqueous solution of the salt gives phenylacetaldehyde, identified by its 2:4-dinitrophenylhydrazone, m. p. 109°. If the reaction mixture is refluxed on a water-bath without removal of the potassium phenylglycidate, the precipitate gradually dissolves. After 3 hours, there separates on cooling a small quantity of the water-soluble *potassium β-hydroxy-α-(o-aminophenylthio)-β-phenylpropionate* (X) (0·25 g.) which crystallises from alcohol in colourless needles, m. p. 209° (Found: C, 55·05; H, 4·55; K, 11·90. $C_{15}H_{14}O_3NSK$ requires C, 55·05; H, 4·32; K, 11·93%). Concentration of the reaction filtrate yields a white solid (1·3 g.) which is a mixture of (IX) and *3-keto-2-(α-hydroxybenzyl)dihydrobenzthiazine* (VIII). The latter compound is also rapidly formed when an aqueous solution of the salt (X) is acidified, and crystallises from aqueous alcohol in colourless needles, m. p. 178—180° (Found: C, 65·9; H, 4·82. $C_{15}H_{13}O_2NS$ requires C, 66·4; H, 4·83%). On being warmed for 5 minutes with dilute sodium hydroxide solution, (VIII) loses benzaldehyde, and acidification then yields 3-ketodihydrobenzthiazine. This decomposition does not occur when (VIII) is boiled with water or dilute acid.

The microanalyses were carried out by N. L. Lottkowitz who reports that the C and H determinations marked with an asterisk were carried out under very humid weather conditions, giving high H results.

The authors wish to express their thanks to Messrs. J. A. Maclaren and W. Savige for experimental assistance, and to Dunlop Rubber (Australia) Ltd. for a research scholarship to one of them (N. S. H.).

UNIVERSITY OF MELBOURNE. [*Received, February 10th*, 1948.]

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67. *The Preparation and Reactions of Aliphatic and Alicyclic Ethylene Sulphides.*

By C. C. J. CULVENOR, W. DAVIES, and N. S. HEATH.

The aliphatic ethylene sulphides often undergo the same ring-opening reactions as do the ethylene oxides, but polymerisation usually prevents the isolation of much of the initial product of ring fission. However, good yields of 2-chlorothiols and 2-chlorothio-esters are obtained by reaction with concentrated hydrochloric acid and acyl chlorides; potassium thioalkoxides and potassium hydrogen sulphide combine readily to form the expected mercapto-sulphides and dithiols; and acetic acid gives a low yield of the 2-mercaptoalkyl acetate.

A characteristic feature of aliphatic ethylene sulphides is the inability of the 3-membered ring to exist with the sulphur atom in the higher-valent state; ring opening always occurs when the preparation of these derivatives is attempted. Sulphoxides and sulphones are not formed, and triethyl- and triphenyl-phosphine and triethyl phosphite remove the sulphur atom to form the ⁞P:S compound. Methyl iodide breaks up ethylene sulphides, the larger ones giving good yields of trimethylsulphonium iodide, the smaller ones mixtures of salts containing small amounts of this iodide.

THE only survey of ethylene sulphides seems to be in the monograph by A. Schönberg in Ahrens Vorträge, Heft 19, Enke, 1933, on "Thioketone, Thioacetale und Aethylensulfide," where, however, the section (pp. 66 to 72) on ethylene sulphides is almost entirely confined to aromatic derivatives.

It has latterly been realised that ethylene sulphides may have industrial applications, *e.g.*, as synthetic polymers, and during the last eight years the results of some technical studies have been described in patents. The present investigation of aliphatic ethylene sulphides deals partly with their preparation, but is chiefly concerned with their reactions and properties, many of which could not have been deduced, by analogy, from a knowledge of the chemistry of ethylene oxides.

Preparation of Ethylene Sulphides.—The first preparations of authentic ethylene sulphides are due to Delépine (*Bull. Soc. chim.*, 1920, **27**, 740), Delépine and Jaffeux (*ibid.*, 1921, **29**,

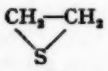
136), and Delépine and Eschenbrenner (*ibid.*, 1923, **33**, 703), who obtained small yields by sodium sulphide treatment of ethylene halothiocyanates or dithiocyanates. This process has been applied by Calingaert (*Bull. Soc. chim. Belg.*, 1922, **31**, 109) and by Youtz and Perkins (*J. Amer. Chem. Soc.*, 1929, **51**, 3508) to make tri- and tetra-methylethylene sulphides. A generally better preparative method is the conversion of ethylene oxides into their sulphur analogues by the use of thiourea, first reported by Dachlauer and Jackel (D.R.-P. 636,708) and extended by Culvenor, Davies, and Pausacker (*J.*, 1946, 1050). It is suitable, however, only for those oxides which have no strongly polar group, such as the carbonyl, next to the oxide ring. High yields are claimed by Coltof (U.S.P. 2,183,860, 1939; B.P. 508,932) by treating 2-chloroethylthiols with weakly alkaline buffered solutions to give ethylene sulphides with little of the polymers which earlier workers had found to be the chief product when concentrated alkali was used. A still more recent method doubtless capable of extension is the dehydration by heat of 1 : 2-dithioglycerol to give mercaptopropylene sulphide (Lazier and Signiago, 1946, U.S.P. 2,396,957). The direct production of ethylene, propylene, and *cyclo*hexene sulphides (Jones and Reid, *J. Amer. Chem. Soc.*, 1938, **60**, 2452) by heating the corresponding olefin with ethyl tetrasulphide—which may provide atomic sulphur—unfortunately gives small yields. In the course of the present investigation it has been found that *cyclo*hexene is not converted into its sulphide by being heated at 440° with molecular sulphur in "Pyrex," and from 440° to 630° in silica with and without iron pyrites as catalyst. The direct catalytic method of synthesis, so valuable in the case of ethylene oxide, is obviously restricted where sulphur compounds are concerned.

The present work on ethylene sulphides makes some statements in the literature seem of questionable value. The preparations of derivatives of ethylene sulphides claimed by Michael (*Ber.*, 1895, **28**, 1633) and Troeger and Hornung (*J. pr. Chem.*, 1897, **56**, 45) are open to doubt from internal evidence. Also we have been unable to repeat the preparation of "αβ-thiocrotonic acid" of Ray and Dey (*J.*, 1917, **111**, 510), and we find that *cyclo*hexene sulphide, b. p. 67—68°/16 mm., can be distilled without difficulty, despite the statement by Mousseron (*Compt. rend.*, 1942, **215**, 201).

Reactions of Ethylene Sulphides.—An outstanding property of ethylene sulphides is the ease, far more pronounced than with ethylene oxides, with which polymers are formed. Delépine and his co-workers were the first to show that lower members of the series gave polymers at ordinary temperatures with water containing traces of acid or alkali.

*cyclo*Hexene sulphide forms polymers in alcohol or aqueous alcohol with hydrazine, hydroxylamine, guanidine, and *o*-aminothiophenol, as well as with other reagents which react normally with ethylene oxides.

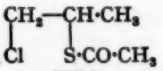
The polymers unavoidably made in the course of the present work vary from viscous distillable liquids to hard non-volatile solids of high molecular weight. The tendency of pure ethylene sulphides to polymerise (which is less pronounced with higher members of the series), according to Coltof and Langedijk (U.S.P. 2,185,660, 1940) can be checked by the presence of hydrogen sulphide and its derivatives, though not by the presence of ordinary antoxidant stabilisers such as quinol. The unit of the polymer from ethylene sulphide itself (I) is probably largely (II).



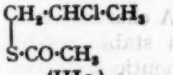
(I.)

$(CH_2 \cdot CH_2 \cdot S)_n$

(II.)



(III.)



(IIIa.)

The polymerisation action of acids can sometimes be controlled by a suitable choice of the conditions of the reaction. An example is the reaction with hydrochloric acid. Delépine (*loc. cit.*), showed that dilute hydrochloric acid instantly polymerised ethylene sulphide to an amorphous powder, whereas the concentrated acid gave a 33% yield of 2-chloroethanethiol. It is now found that excess of concentrated hydrochloric acid at room temperature converts *cyclo*hexene and chloropropylene sulphides into the 2-chlorothiols in 57% and 72% yields respectively, if the reaction mixture is homogenised by mechanical shaking, while polymer is the major product if the reaction is carried out (*a*) at the boiling point, (*b*) by mixing without thorough shaking, or (*c*) by passing hydrogen chloride gas into the sulphide.

Sulphuric acid, dilute or concentrated, appears to exert only a polymerising influence, though this may be due to the instability of the monothioethylene glycol product to acid (cf. Bennett, *J.*, 1922, **121**, 2144). With excess of boiling glacial acetic acid, *cyclo*hexene sulphide gives 2-*mercapto*cyclo*hexyl acetate* and 2-*mercapto*cyclo*hexyl* 2-*acetoxy*cyclo*hexyl sulphide*.

Acetyl chloride combines readily with ethylene sulphides at ordinary temperatures to give excellent yields of the 2-chloro-thiolacetates. In this way *cyclo*hexene sulphide gives 2-*chloro*-cyclo*hexyl thiolacetate*. The question whether the *chloropropyl thiolacetate* from propylene sulphide, and the *dichloropropyl thiolacetate* from chloropropylene sulphide are derivatives of *iso*propylthiol (as III) or of *n*-propylthiol (as III*a*) is under investigation. Benzoyl chloride reacts more slowly than acetyl chloride with propylene sulphide, and gives a high yield of a *2-chloropropyl thiolbenzoate*. Aldermann, Brubaker, and Hanford (U.S.P. 2,212,141, 1940) have already converted ethylene sulphide itself into 2-chloroethyl thiolacetate and 2-acetoxyethyl thiolacetate, by the action of acetyl chloride, and of acetic anhydride with pyridine, respectively. We find that the ethylene sulphides used (chiefly propylene and *cyclo*hexene sulphides) merely form polymers with the following halogen compounds: benzoyl fluoride, picryl chloride, 3 : 5-dinitrobenzoyl chloride, triphenylmethyl chloride, and toluene-*p*-sulphonyl chloride and fluoride.

*cyclo*Hexene sulphide is polymerised by aqueous alkali and by excess of concentrated aqueous ammonia, but reacts with methylaniline to form *2-methylanilino*cyclo*hexylthiol*. The nature of the product and also the catalytic effect on the reaction of hydroxy-compounds such as ethanol, clearly bring out the analogy between ethylene oxides and sulphides. Reppe and Nicolai (D.R.-P. 631,016; "Friedländer," XXIII, 244) describe the reaction of ethylene and propylene sulphides at high temperatures with primary and secondary amines, and the expected 2-aminothiol is the chief product. Organometallic compounds also seem to react in the expected way; thus ethylene sulphide and diethylaminelithium give 2-diethylaminoethylthiol (Gilman and Woods, *J. Amer. Chem. Soc.*, 1945, **67**, 1843).

It has recently been shown (Culvenor, Davies, and Heath, preceding paper) that ethylene oxides are remarkably reactive with soluble metallic derivatives of R·SH, and ethylene sulphides are now found to be similarly reactive. Potassium hydrogen sulphide converts *cyclo*hexene and propylene sulphides into the corresponding dithiols, while from chloropropylene sulphide is obtained a small amount of trithioglycerol. Simple alkali thioalkoxides also combine with *cyclo*hexene sulphide, and in this way are obtained *ethyl* and tert.-*butyl* 2-*mercapto*cyclo*hexyl sulphides*; in each case considerable amounts of higher condensed products were formed.

It is now seen that the powerful polymerising action of sodium hydroxide or other strongly alkaline reagents (NaX) is due to the conversion of a molecule of ethylene sulphide into $NaS{\cdot}CH_2{\cdot}CH_2X$, which then opens another sulphide ring to form $NaS{\cdot}CH_2{\cdot}CH_2{\cdot}S{\cdot}CH_2{\cdot}CH_2X$, a long chain then being rapidly formed. Such polymerisation with alkaline reagents can be prevented when the reagent (*e.g.*, potassium xanthate) is so constituted that the condensation product with one molecule of ethylene sulphide can yield a stable cyclic compound such as trithiocarbonate (Culvenor, Davies, and Pausacker, *loc. cit.*).

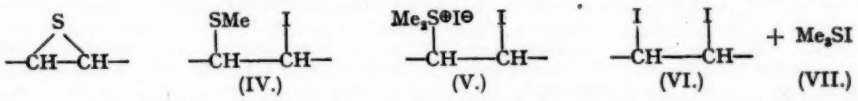
Some very recent technical applications of ethylene sulphides are noteworthy. Barr and Speakman (*J. Soc. Dyers and Col.*, 1944, **60**, 238) and Blackburn and Phillips (*ibid.*, 1945, **61**, 203) describe the modification of wool fibres with ethylene sulphide, and Lazier and Signiago (*loc. cit.*) combine mercaptopropylene sulphide with both natural and synthetic polymers. From the foregoing account of ethylene sulphides it is clear that they may be capable of reacting with the amino- or thiol groups in natural proteins such as wool, or with the hydroxy-groups (causing polymerisation) in cellulose fibres.

A characteristic unsuspected property of the ethylene sulphide ring is its inability to exist in a stable condition when the sulphur atom has a higher valency than two. The only authentic instances of such compounds are the very unstable tetraphenylethylene sulphone of Staudinger and Pfenninger (*Ber.*, 1916, **49**, 1946) and the equally unstable diphenyldiethylethylene sulphones of Vargha and Kovacs (*Ber.*, 1942, **75**, 794). All these were prepared from sulphur dioxide and the corresponding substituted diazomethane. The instability of these sulphones contrast with the stability of the sulphones, formed by direct oxidation, of 3 : 4-diphenyl- and tetraphenyl-thiophens (Hinsberg, *Ber.*, 1915, **48**, 1612). The present investigations show that whereas thiophens do not form higher-valent sulphur derivatives other than sulphones, the sulphur in aliphatic ethylene sulphides is most prone to become higher-valent, but the three-membered ring undergoes fission in the process. Thus thiophen and ethylene sulphides are anomalous, though for different reasons.

*cyclo*Hexene and 4-methyl*cyclo*hexene sulphides slowly react at ordinary temperature with a slight excess of methyl iodide to form, in about 50% yield, trimethylsulphonium iodide (VII). This is also formed from chloropropylene sulphide and propylene sulphide, in the latter case only when a large excess of methyl iodide is used. The reaction with ethylene sulphide has been studied by Delépine (*Bull. Soc. chim.*, 1920, **27**, 743), who isolated a salt of the approximate

composition $(C_2H_4S)_3,CH_3I$. The anlysis did not agree with this or any other formula, and the product is undoubtedly a mixture. These statements apply equally to Delépine and Jaffeux's product (*loc. cit.*) from propylene sulphide and methyl iodide.

Trimethylsulphonium iodide is formed less easily from low-molecular ethylene sulphides than from higher ones. It is known that the iodine in higher aliphatic iodides is generally less reactive than in lower ones, and consequently, when *cyclo*hexene sulphide is used, the derived iodide (IV) will be inert compared with methyl iodide. Hence (VII) will be ultimately formed;



(IV.) (V.) (VI.) (VII.)

but when, say, propylene sulphide is used with only a small excess of methyl iodide, the selective action of the latter on (IV) will not be so pronounced, because it will now be in competition with the moderately reactive methyl iodopropyl sulphide (as IV). This could react with itself, or with unchanged propylene sulphide, and so form a complex mixture of salts (see p. 287). This effect would be diminished by increasing the proportion of methyl iodide, and, in fact, (VII) can be isolated only when a large excess (20 to 30 mols.) of methyl iodide is used. The above considerations explain why Delépine (*loc. cit.*) obtained a mixture of salts from ethylene and propylene sulphides and methyl iodide.

The formation of trimethylsulphonium iodide from the interaction of thioethers and methyl iodide is described by Ray and Levine (*J. Org. Chem.*, 1937—1938, **2**, 267), and further references to this type of fission are Farmer and Shipley (*J. Polymer Sci.*, 1946, **1**, 293; *J.*, 1947, 1531) and Naylor (*J.*, 1947, 1107). It is abundantly clear from the present investigation that, when a thio-compound and methyl iodide form a simple addition compound, ·SMeI, this clearly indicates that the original thio-compound was not an ethylene sulphide. Thus the product, $C_{10}H_{16}S$, from pinene and sulphur is unlikely to have the ethylene sulphide ring assumed by Budnikoff and Schilow (*Ber.*, 1922, **55**, 3850) because they show that methyl iodide forms $C_{10}H_{16}S,MeI$. Similarly, the methyl iodide method of examining the sulphur linkage in vulcanised rubber (Westlake, *Chem. Reviews*, 1946, **39**, 233; Selker and Kemp, *Ind. Eng. Chem.*, 1944, **36**, 22) now requires reconsideration in view of the possibility of the presence of ethylene sulphide groups.

The reaction between methyl iodide and ethylene sulphides has a very limited analogy in the ethylene oxide series, where the conditions have to be drastic to bring about any reaction at all. The oxide ring can be opened; *e.g.*, methyl iodide with epichlorohydrin at 190° for 5 hours gives $CH_2Cl{\cdot}CHI{\cdot}CH_2{\cdot}OMe$ (Paul, *Ber.*, 1888, **21**, 2971), and with *cyclo*hexene oxide at 150—160° for 48 hours gives 2-iodo*cyclo*hexyl methyl ether (Bedos, *Compt. rend.*, 1926, **183**, 563).

Ethylene sulphides react at ordinary temperatures with chloramine-T to form opaque, thick liquids but no sulphilimine. Ethylene, propylene, chloropropylene, *iso*butylene, and *cyclo*hexene sulphides at ordinary temperatures lose their sulphur to triethylphosphine, the crystalline triethylphosphine sulphide being isolated. Similarly triphenylphosphine sulphide and triethyl thiophosphate are formed by interaction of *cyclo*hexene sulphide with triphenylphosphine and triethyl phosphite respectively. *cyclo*Hexene and propylene sulphides give viscous liquids with methyl sulphate, and the former reacts with chlorine in carbon tetrachloride to form 1 : 2-dichloro*cyclo*hexane, together with polymeric material. Hydrogen peroxide reacts very readily with ethylene sulphides (the explosive "peroxide" of acetone is formed when acetone is used as solvent), but sulphoxides or sulphones cannot be isolated by the use of either aqueous peroxide or permanganate. Delépine and Eschenbrenner (*loc. cit.*) have shown that oxidation of ethylene sulphide with concentrated nitric acid leads to sulphoacetic acid, $SO_3H{\cdot}CH_2{\cdot}CO_2H$, and other more condensed acids of which the acid

$$SO_3H{\cdot}CH_2{\cdot}CH_2{\cdot}S{\cdot}CH_2{\cdot}CO_2H$$

was characterised.

An instantaneous reaction is given with aqueous mercuric salts, but as the precipitates cannot be purified they have little theoretical implication. All the above experiments, carried out with the object of making derivatives of ethylene sulphides in which the higher valency of sulphur is invoked, can be explained by the fission of the ethylene sulphide ring.

Experimental.

Opening of Ethylene Sulphides by Hydroxy-compounds.—At ordinary temperatures, ethylene sulphides are fairly stable to neutral water and alcohols. However, ethylene sulphides instantly produce nitrogen

when treated with aqueous sodium azide and iodine, showing that at least a trace of a thiol is immediately formed (Feigl, "Spot Tests," Nordemann, 1937, p. 241; *Z. anal. Chem.*, 1928, **74**, 369). Propylene sulphide, heated with 2 mols. of water at 100° for 17 hours in a sealed tube, forms a mixture of products, some of which can be distilled at high temperatures. The same conditions with absolute ethyl alcohol give similar though more fragrant products, and in both experiments a considerable gas pressure is produced.

2-*Chloro*cyclo*hexylthiol*, b. p. 83°/20 mm., $n_D^{20°}$ 1·5015, is obtained when *cyclo*hexene sulphide (10 g.) is shaken continuously with concentrated hydrochloric acid (100 ml.) for twelve hours, and the product extracted with chloroform, washed once with water, dried, and distilled. Yield, 7·5 g.; 57% (Found: C, 48·2; H, 7·4. $C_6H_{11}ClS$ requires C, 47·8; H, 7·3%). The oil liberates carbon dioxide very slowly from sodium hydrogen carbonate solution, and is converted into *cyclo*hexene trithiocarbonate by potassium xanthate. Similarly, a *dichloropropylthiol*, b. p. 81°/33 mm. (9·6 g.; 72% yield), of which the structure is under investigation, is formed when chloropropylene sulphide (10 g.) and concentrated hydrochloric acid (120 ml.) are shaken for 12 hours and worked up as above (Found: S, 22·4. $C_3H_6Cl_2S$ requires S, 22·1%).

Acetic Acid and cyclo*Hexene Sulphide.*—*cyclo*Hexene sulphide (5 g.) and glacial acetic acid (15 ml.) are rapidly mixed in the cold and added as quickly as possible to boiling glacial acetic acid (20 ml.) through the condenser. The addition is regulated so that the mixture remains boiling, and, when complete, the refluxing is continued for 45 minutes. Fractionation of the product gives, after a small low fraction, 2-*mercapto*cyclo*hexyl acetate* (2 g., 26%), b. p. 109°/15 mm. (Found: C, 55·6; H, 8·33. $C_8H_{14}O_2S$ requires C, 55·2; H, 8·05%), and 2-*mercapto*cyclo*hexyl* 2-*acetoxy*cyclo*hexyl sulphide* (3 g., 48%), b. p. 165°/0·7 mm. (Found: C, 57·9; H, 8·5. $C_{14}H_{24}O_2S_2$ requires C, 58·3; H, 8·3%), with very little higher-boiling residue. The low fractions redistilled four times gave each time a pink distillate, which became colourless after 30 minutes.

To ensure that the oil of b. p. 109°/15 mm. was not the diacetyl derivative, the latter compound was made by acetylation of 2-mercapto*cyclo*hexanol (Culvenor, Davies, and Heath, *loc. cit.*). 2-Mercapto*cyclo*hexanol (5 g.) was dropped slowly into acetyl chloride (7·5 g., 50% excess) with cooling, and the mixture heated for 2 hours at 50° under reflux. Distillation yielded 2-*mercapto*cyclo*hexanol diacetate* (7·6 g., 93%), b. p. 145°/19 mm. (Found: S, 15·0. $C_{10}H_{16}O_3S$ requires S, 14·81%).

Addition of Potassium Hydrogen Sulphide to Sulphides.—The sulphide (0·2 mol.) is added with shaking to potassium hydrogen sulphide prepared by saturating a solution of potassium hydroxide (1·1 g.) in alcohol (12 ml.) with hydrogen sulphide at 0°. After 24 hours, the mixture is diluted with water, acidified, and extracted with chloroform. Propylene sulphide gives propylenedithiol (0·5 g.), b. p. 72—74°/55 mm., *cyclo*hexene sulphide gives *cyclo*hexenedithiol (1·1 g., 38%), b. p. 97°/15 mm. (Culvenor and Davies, *Australian J. of Scientific Research*, 1948, **1**, 236), while from chloropropylene sulphide and excess of potassium hydrogen sulphide is obtained a small amount of trithioglycerol, b. p. 112—120°/14 mm., identified by conversion into the trimethyl ether trisulphone, m. p. 203° (Rheinboldt and Tetsch, *Ber.*, 1937, **70**, 675).

Addition of Thioalkoxides to Ethylene Sulphides.—Free thiols do not easily open the ethylene sulphide ring; *e.g.*, *cyclo*hexene sulphide and ethylthiol, after being heated in a sealed tube at 120° for 6 hours, are recovered unchanged except for a very small amount of non-distillable oil. In the presence of a mol. of alkali, however, reaction occurs readily. *cyclo*Hexene sulphide (5·5 g.) is added with shaking to a solution prepared by adding the thiol in small excess to alcoholic potassium hydroxide (2·8 g.) in alcohol (15 ml.). The mixture is cooled till no more heat is evolved, then left overnight and worked up as in the potassium hydrogen sulphide reaction. Ethylthiol gives in this way 2-*mercapto*cyclo*hexyl ethyl sulphide* (4·7 g., 55%), b. p. 124°/20 mm. (Found: C, 54·4; H, 8·9. $C_8H_{16}S_2$ requires C, 54·5; H, 9·16%), and 2-*mercapto*cyclo*hexyl* 2-*ethylthio*cyclo*hexyl sulphide* (1·8 g., 30%), b. p. 152°/0·25 mm. (Found: C, 57·6; H, 9·1. $C_{14}H_{26}S_3$ requires C, 57·9; H, 9·03%). *tert.*-Butylthiol gives 2-*mercapto*cyclo*hexyl* tert.-*butyl sulphide* (2·5 g., 25%), b. p. 133°/12 mm. (Found: C, 58·5; H, 9·8. $C_{10}H_{20}S_2$ requires C, 58·8; H, 9·8%), and 2-*mercapto*cyclo*hexyl* 2-tert.-*butylthio*cyclo*hexyl sulphide* (2·0 g., 25%), b. p. 187—188°/1 mm. (Found: C, 59·9; H, 9·3. $C_{16}H_{30}S_3$ requires C, 60·4; H, 9·4%).

Polymeric material is formed in all these reactions, and this is the only product when mercaptobenzthiazole is used.

Acyl Chlorides and Ethylene Sulphides.—Addition is effected by mixing the sulphide and acyl chloride in equimolecular amounts with cooling when necessary. After being left overnight, the product is distilled. Propylene sulphide and acetyl chloride give a *chloropropyl thiolacetate*, b. p. 84·5°/21 mm. (Found: C, 39·0; H, 5·5. C_5H_9OClS requires C, 39·5; H, 5·9%); propylene sulphide and benzoyl chloride give a *chloropropyl thiolbenzoate*, b. p. 117°/0·2 mm. (Found C, 56·15; H, 5·05. $C_{10}H_{11}OClS$ requires C, 56·1; H, 5·3%). *cyclo*Hexene sulphide and acetyl chloride give 2-*chloro*cyclo*hexyl thiolacetate*, b. p. 110°/20 mm. (Found: Cl, 18·5. $C_8H_{13}OClS$ requires Cl, 18·4%); and chloropropylene sulphide and acetyl chloride combine with very little heat evolution to form a *dichloropropyl thiolacetate*, b. p. 115°/18 mm., $n_D^{20°}$ 1·5157 (Found: C, 32·0; H, 4·28. $C_5H_8OCl_2S$ requires C, 32·1; H, 4·28%).

2-*Methylanilino*cyclo*hexylthiol* (2 g.; 50% yield), a yellow oil, b. p. 175°/16 mm., is formed when *cyclo*hexene sulphide (2 g.) and methylaniline (2 g.) are refluxed in 80% alcohol (15 ml.) for 8 hours, poured into water, and extracted with ether (Found: S, 14·7. $C_{13}H_{19}NS$ requires S, 14·5%). It is not obtained when the reactants are heated at 100° for 24 hours without a solvent.

Reaction of Ethylene Sulphides with Methyl Iodide.—cyclo*Hexene sulphide. cyclo*Hexene sulphide (1·1 g.) is mixed with dry methyl iodide (1·5 g.) and left at room temperature. After 48 hours the dark brown solid containing iodide is filtered off, washed with dry acetone, and recrystallised from absolute alcohol to give white needles of trimethylsulphonium iodide, m. p. 215°. If excess of methyl iodide (5 g.) be used, after 2 weeks the yield of trimethylsulphonium iodide is 1 g. (50%) (Found: I, 62·8; S, 15·2. Calc. for C_3H_9SI: I, 62·3; S, 15·6%). The iodide gave no m. p. depression on admixture with an authentic specimen. No success met attempts to isolate the unknown 1:2-di-iodo*cyclo*hexane from the reaction mixture. Similarly 4-methyl*cyclo*hexane sulphide (1·2 g.) gave 1·0 g. of trimethylsulphonium iodide.

Chloropropylene sulphide. Chloropropylene sulphide (1·1 g.) is refluxed with excess (5 g.) of dry methyl iodide. Trimethylsulphonium iodide slowly crystallises from the reaction mixture and is obtained pure by the procedure above. The reaction occurs also at room temperature, but is much slower than that of *cyclo*hexene sulphide.

Propylene sulphide. Propylene sulphide, left at room temperature with a moderate excess of dry methyl iodide, deposits a white, unstable, crystalline salt which decomposes in the range 70—90°. This material soon decomposes if left in the air, and although it can be recrystallised from absolute alcohol by working quickly, or by solution in absolute alcohol and precipitation with dry ether, consistent analyses are not obtained. A series of products gave (Parr bomb process with Na_2O_2) I from 41·2% to 68·5%, and S, on one sample only, 7·7%. Delépine (*loc. cit.*) found I, 47·7%. The simple addition formula C_3H_6S,CH_3I, requiring I, 58·8; S, 14·8%, as well as more complex addition formulæ, are clearly untenable. If the reaction time is prolonged no crystalline material is obtained, the darkening is more pronounced, and, if the reaction mixture is tightly stoppered, a considerable gas pressure develops.

Propylene sulphide and a large excess of methyl iodide. If propylene sulphide is added in small lots (0·5 g.) daily to dry methyl iodide (140 g., about 20 mols.), after three or four additions a salt crystallises out which is much more stable. After the product has been washed with acetone and recrystallised from absolute alcohol three or four times, pure trimethylsulphonium iodide, m. p. 215°, is obtained, identified as above.

Ethylene sulphide. On being kept at room temperature with a moderate excess of methyl iodide, ethylene sulphide gives a mixture of salts decomposing about 60° (Found: S, 11·0%. Delépine gives I, 37·9%. Neither result agrees with the simple addition formula, C_2H_4S,MeI requiring I, 62·9; S, 15·8%, or with other possible addition formulæ).

Ethylene Sulphides and Tervalent Phosphorus Compounds.—Ethylene, chloropropylene, propylene, and *cyclo*hexene sulphides when mixed with a slight excess of triethyl phosphine and left at room temperature for 2 days, deposit needles of triethylphosphine sulphide, m. p. 90°. In the case of ethylene and propylene sulphide, cooling is necessary to avoid polymerisation, while for *iso*butylene sulphide the main product is amorphous, but, by solution in toluene and careful evaporation, some triethylphosphine sulphide can be obtained.

Triethyl phosphite (3 g.) and *cyclo*hexene sulphide (2 g.) are kept at room temperature a week, heated on the water-bath for an hour, and fractionated under reduced pressure. Triethyl thiophosphate, b. p. 104°/20 mm., is obtained as the main fraction; this is identical with a sample obtained by the method of Strecker and Spitaler (*Ber.*, 1926, **59**, 1772), who record b. p. 95·5°/12 mm.

*cyclo*Hexene sulphide (1·5 g.) and triphenylphosphine (2·6 g.) are mixed in carbon disulphide or chloroform (10 ml.); after 3 days the solvent is removed and the white solid residue recrystallised from absolute alcohol to give white needles of triphenylphosphine sulphide, m. p. 158°. This gave no m. p. depression on admixture with a sample of the sulphide prepared by the method of Michaelis *et al.* (*Ber.*, 1882, **15**, 803; *Annalen*, 1885, **229**, 307).

Reaction of cyclo*Hexene Sulphide and Chlorine.*—*cyclo*Hexene sulphide diluted with an equal volume of carbon tetrachloride is added drop by drop with cooling to a slight excess of a chlorine–carbon tetrachloride solution. After the mixture has been left overnight and distilled, a fraction, b. p. 82°/18 mm., is obtained, containing chlorine but no sulphur, and with $n_D^{18°}$ 1·4893, as well as a large amount of polymeric material which will not distil. This lower fraction on being kept with potassium hydroxide and *o*-aminothiophenol gives hexahydrophenthiazine, m. p. 81° (Culvenor, Davies, and Heath, *loc. cit.*), and hence is concluded to be 1 : 2-dichloro*cyclo*hexane which has $n_D^{16°}$ 1·4886, b. p. 187—190°/760 mm.

Microanalyses were carried out by N. L. Lottkowitz. The authors wish to express their thanks to Messrs. P. F. Nelson and J. A. Maclaren for experimental assistance, and to Dunlop Rubber, Australia, Ltd., for a research scholarship to one of them (N. S. H.).

UNIVERSITY OF MELBOURNE. [*Received, February 10th*, 1948.]

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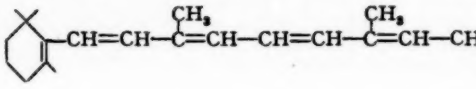
68. *Studies in the Polyene Series. Part XXV. Molecular Structure and Vitamin-A Activity. The Synthesis of a Biologically Active C_{17} Acid.*

By SIR IAN HEILBRON, E. R. H. JONES, and R. W. RICHARDSON.

The relationship between molecular structure and vitamin-A activity is briefly discussed, and schemes for the synthesis of analogues of vitamin A with simplified structures are outlined. A novel synthesis of a C_{17} acid (IX), isolated in two geometrically isomeric forms, containing an acetylenic bond in the side chain and an otherwise unsubstituted *cyclo*hexene ring is described. One of these isomers, administered orally to young rats as the sodium salt, exhibits activity approximately one-thousandth of that of vitamin A itself.

BECAUSE of the difficult character of synthetic work on polyenes of the vitamin-A type, most of the information which is available at present concerning the relationship between molecular structure and vitamin-A activity has been accumulated from growth promotion tests with the naturally occurring carotenoid pigments and their degradation products and, to a lesser extent, with transformation products of the vitamin itself (cf. Jones, *Ann. Reports*, 1940, **37**,

290). The structural variations possible with the natural materials and derived substances are rather limited; few alterations involving the carbon skeleton have been possible, the main changes having been concerned with cyclic or open-chain structures (*e.g.*, β-carotene and lycopene), the presence or otherwise of oxygen-containing groups in the cyclic portion of the molecule (*e.g.*, xanthophylls), the length of the conjugated system (carotenes, *apo*carotenals, and vitamin A), geometrical isomerism, etc. The results available, however, from the tests on carotenoids and their degradation products, do not necessarily afford a true picture of the



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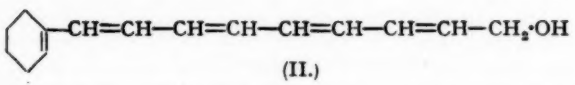

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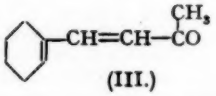


(III.)

effect of variations in molecular structure on vitamin-A activity, since structural factors may determine the mode of fission of carotenoid molecules in the animal body. The failure of a carotenoid to promote growth may be attributable to its inability to undergo fission in the required manner rather than to the inherent inactivity of its breakdown products. In this connexion there is some evidence to indicate that certain carotenoids may function directly (*i.e.*, without breakdown) as vitamins for some animals (Pirie and Wood, *Biochem. J.*, 1946, **40**, 557; With, *Nature*, 1946, **157**, 627).

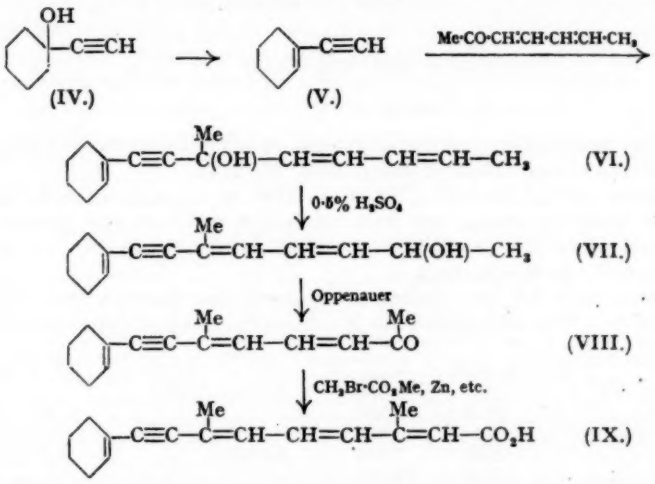
Until recently, the number of synthetic substances of indubitable structure which have been available for animal tests has been almost insignificant, due to the seemingly insuperable difficulties which have faced investigators in this field (cf. Jones, *Ann. Reports*, 1941, **38**, 170). In the last few years, however, following the discovery and development of new synthetic methods applicable in the polyene field, several routes leading to the synthesis of vitamin A and closely related compounds have been described (for summary see Heilbron, Pedler Lecture, *J.*, 1948, 386), and it is now possible to envisage the synthesis of a considerable number of polyenes of the vitamin-A type in a state of absolute purity. From biological tests on such substances much information concerning the relationship between molecular structure and biological activity will be forthcoming; it seems not unlikely that Nature will be found to have been over-elaborate in designing the vitamin-A molecule, and that substances with similar but simpler structures may exhibit considerable biological activity.

In this and subsequent papers in this series, we shall describe researches which have as their objective the synthesis of a variety of analogues of vitamin A (I) with simplified structures. An extreme example is the C_{15} alcohol (II), containing the same conjugated system as the natural vitamin, but none of the side-chain and ring-methyl groups. In other examples some of these methyl groups will be reintroduced, variations will be made in the ring system and in the terminal functional group, and the substitution of ethylenic by acetylenic bonds in the side chain and the effect of geometrical isomerism will be studied. Since all the successful syntheses recently reported have utilised β-ionone as starting material, in order to achieve our objectives we had either to synthesise the analogous ketone (III), devoid of methyl groups, or to devise a new synthesis of an entirely novel type. Both of these approaches have been successful, and the synthesis of the ketone (III), in which we have been interested for some years in connexion with light absorption studies, will be described in a later paper. Attention is now mainly directed to a new synthetic approach to compounds of the vitamin-A type by a route which, because of its simplicity and adaptability, appears to be eminently suited to our present purpose of preparing a variety of structural variants of the vitamin-A molecule.

Two crystalline geometrically isomeric C_{17} acids (IX) have been synthesised by the following route, the yields obtained at the various stages have been reasonably satisfactory, and the starting materials are all readily available. The dehydration of the ethynyl*cyclo*hexanol (IV) to ethynyl*cyclo*hexene (V)* proved to be the critical stage in the synthesis because of the ease with which three alternative reactions can take place. These are dehydration and isomerisation to ethylbenzene (particularly at high temperatures), isomerisation to acetyl*cyclo*hexene (under acidic conditions), and fission to *cyclo*hexanone and acetylene (especially over basic

* *Added in Proof.*—Since this paper was written, Milas *et al.* (*J. Amer. Chem. Soc.*, 1948, **70**, 1292, 1829) and Sobotka and Chanley (*ibid.*, p. 3914) have described the preparation of (V) and its use in the synthesis of compounds related to vitamin A.

catalysts). Previous claims (Merling, D.R.P. 280,226; Carothers and Coffman, *J. Amer. Chem. Soc.*, 1932, **54**, 4071) for the satisfactory preparation of the hydrocarbon (V) could not be substantiated, but we have now found that by passing the vapours of the carbinol (IV) over aluminium phosphate at 300—310°, preferably under reduced pressure, almost pure



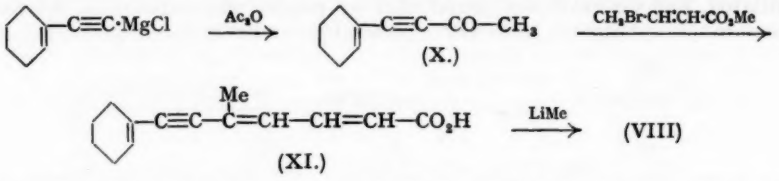
ethynyl*cyclo*hexene (V) can be obtained in conversions up to 55%, the greater part of the residue being unchanged carbinol. That our product is truly the acetylenic hydrocarbon has been amply confirmed by silver salt determination, quantitative hydrogenation, light-absorption measurements, ozonolysis, and partial hydrogenation to the known vinyl*cyclo*hexene.

The Grignard reagent from the hydrocarbon (V) was condensed with crotonylideneacetone by a method similar to that previously employed (Cymerman, Heilbron, and Jones, *J.*, 1944, 144) for the condensation of αβ-unsaturated ketones with hex-1-yne, and gave the *carbinol* (VI) in 55% yield. [Crotonylideneacetone prepared from crotonaldehyde and acetone by the method of Meerwein (*Annalen*, 1908, **358**, 85; see also Rapson and Shuttleworth, *J.*, 1940, 636) was found to be non-homogeneous, distillation effecting but little purification. By washing the crude product with water or by omitting Meerwein's salting out procedure, the pure ketone was readily obtained.] As was expected the carbinol (VI) underwent anionotropic rearrangement on being shaken with 0·5% sulphuric acid (cf. Heilbron, Jones, *et al.*, *J.*, 1943—1946), the fully conjugated *carbinol* (VII) (**3** : *5-dinitrobenzoate*), obtained in 75% yield, exhibiting light-absorption properties consistent with the quadruple conjugation. The *ketone* (VIII) was prepared from the rearranged carbinol by Oppenauer oxidation, using aluminium *tert.*-butoxide and acetone, being regenerated from the *semicarbazone* by the procedure used by Heilbron, Jones, and O'Sullivan (*J.*, 1946, 866).

The same ketone has also been synthesised, although rather less conveniently, by an alternative route similar to that employed by Arens and van Dorp (*Rec. Trav. chim.*, 1946, **65**, 338; cf. also Heilbron, Jones, and O'Sullivan, *loc. cit.*) for the synthesis of the structurally analogous C_{18} ketone of the vitamin-A series. *cyclo*Hexenylethynylmagnesium chloride was condensed with acetic anhydride at low temperatures (−60° to −0°) to give the *ketone* (X), characterised by a number of derivatives. The ketone exhibited the expected light-absorption properties, and hydrogenation gave cyclo*hexylbutan-2-one* which on oxidation with hypobromite yielded the known β-*cyclo*hexylpropionic acid. The Reformatsky reaction between the acetylenic ketone (X) and methyl ω-bromocrotonate proceeded rather unsatisfactorily, much decomposition occurring even in dilute solutions, and after dehydration of the crude hydroxy-ester with anhydrous oxalic acid, followed by hydrolysis, the crystalline *acid* (XI) was isolated in only 5% yield. Treatment of this acid with methyl-lithium in ethereal solution (cf. Arens and van Dorp, *loc. cit.*) gave the ketone (VIII) (85% yield), identical with that obtained by the alternative route described above.

Condensation of (VIII) with methyl bromoacetate and zinc, and dehydration and hydrolysis of the crude hydroxy-ester, gave the C_{17} *acid* (IX) which was readily isolated in two forms, m. p. 179° (20% yield) and m. p. 152° (10% yield), by fractional crystallisation. Since they are both derived from the same C_{18} ketone, these acids are probably geometrical isomerides

about the terminal double bond, as in the case of vitamin A and *neo*vitamin A (Robeson and Baxter, *J. Amer. Chem. Soc.*, 1947, **69**, 136). Their light-absorption properties are practically



identical, secondary maxima due to the acetylenic system effectively preventing the detection of any *cis*-peak (Zechmeister, *Chem. Reviews*, 1944, **34**, 267).

When the sodium salt of the acid (IX), m. p. 179°, in aqueous solution buffered at pH 10, was administered orally to young rats on a vitamin-A deficient diet, growth responses were produced at doses which indicated that the acid exhibited activity of the order of one-thousandth of that of vitamin A itself.

Light-absorption data for the various compounds described in this paper are collected together in the Table. Ethynyl*cyclo*hexene (V) shows the characteristic maximum and inflexion

	$\lambda_{max.}$ A.	$\epsilon_{max.}$		$\lambda_{max.}$ A.	$\epsilon_{max.}$
Ethynyl*cyclo*hexene (V)	2230	12,500	Ketone (VIII)	3350	23,000
	2280 *	9,500		2450	18,000
Dimethylvinylacetylene [1]	2195	9,000	C_{18} ketone [4]	3350	38,000
	2260 *	7,000	Acid (XI)	3130	22,000
Carbinol (VI)	2270	39,000		2370	16,500
	2370	30,000		2420 *	14,500
Carbinol (VII)	2910	21,500	C_{17} acid [4]	3250	32,500
	3060	15,000	Acid A (IX)	3390	27,500
Decatetraenol [2]	2985	64,000		2600	12,000
	3110	64,000		2570	11,000
HC:C·[CH:CH]$_3$·CH(OH)·CH$_3$ [3]	2920	60,000	Acid B (IX)	3420	31,000
	3050	54,000		2600	9,500
	2790	40,000	Vitamin A acid [5]	3400	37,500

* Inflexion.

[1] Jones and McCombie, *J.*, 1943, 261. [2] Reichstein and Trivelli, *Helv. Chim. Acta*, 1932, **15**, 1074.
[3] Heilbron, Jones, and McCombie, *J.*, 1944, 134. [4] Heilbron, Jones, and O'Sullivan, *J.*, 1946, 866.
[5] Arens and van Dorp, *Rec. Trav. chim.*, 1946, **65**, 338.

observed with conjugated vinylacetylenes, and the carbinol (VI) exhibits high-intensity absorption in the 2300 A. region consistent with the presence of conjugated diene and enyne systems in the molecule. The light-absorption properties of the rearranged carbinol (VII) are similar to those of other compounds containing four unsaturated linkages in conjugation, and those of the ketone (VIII) and the two acids (XI) and (IX) approximate closely to those of the corresponding compounds synthesised from β-ionone (Arens and van Dorp, *loc. cit.*; Heilbron, Jones, and O'Sullivan, *loc. cit.*).

The number of variations which are possible on the synthetic schemes outlined in this paper are considerable. Ring methyl groups can readily be introduced by preparing the ethynylcarbinols from mono-, di-, and tri-methyl*cyclo*hexanones followed by dehydration to give homologues of ethynyl*cyclo*hexene (V). The side-chain methyl group in the carbinol (VI) and the subsequent products can be eliminated by employing sorbaldehyde in place of crotonylideneacetone with the Grignard reagents from ethyl*cyclo*hexenes. Since the anionotropic rearrangement involved in the conversion of (VI) into (VII) is of such a general nature (cf. Jones, *Ann. Reports*, 1944, **41**, 148), the extent of the conjugated system in the final product can be varied at will by utilising aldehydes and ketones such as, *e.g.*, ethylideneacetone and octatrienal for building up the major portion of the side chain.

The partial hydrogenation of the acetylenic linkage, using a palladium catalyst with diminished activity, could probably be effected in the final products [*e.g.*, the acid (IX)], but it would almost certainly be more effective if carried out on the intermediate carbinol (VI) before rearrangement. As has already been indicated the Reformatsky reaction involved in the final stage of the synthesis of the acid (IX) leads to the production of *cis–trans* isomers, presumably about the terminal ethylenic linkage. It is possible that the development of improved methods for the partial reduction of the acetylenic linkage may also permit of the controlled production of geometrical isomerides.

Much variation in the nature of the terminal functional group can be achieved by employing the new methods which are now available. Thus the carboxyl group in (IX) could be reduced to a primary alcohol group by using lithium aluminium hydride (Nystrom and Brown, *J. Amer. Chem. Soc.*, 1947, **69**, 2548), while the corresponding aldehyde and the same primary alcohol could be prepared by taking advantage of the procedure devised by Arens and van Dorp (*Nature*, 1947, **160**, 189) involving the condensation of the ketone (VIII) with ethoxyacetylene.

The ready availability of the ketone (III), a lower homologue of β-ionone, permits of additional alternative syntheses based on the now established routes to polyenes of the vitamin-A type. In this case also, the possibility of progressive introduction of ring methyl groups can be envisaged.

The considerable progress that has already been made in work along several of the lines outlined above will be reported in later papers in this series.*

Experimental.

Light-absorption measurements were carried out in ethanol except where stated otherwise. All the operations were carried out in an atmosphere of nitrogen.

Ethynylcyclohexene (V).—Ethynyl*cyclo*hexanol (100 g.; prepared by a method similar to that used by Heilbron, Jones, and Weedon, *J.*, 1945, 83) was distilled slowly (*ca.* 25 g./hr.) in nitrogen at 120—130° (bath temp.)/40 mm. through a " Pyrex " tube (70 × 2 cm.) containing a supported aluminium phosphate catalyst kept at 300—310°. The catalyst was prepared by immersing pieces of porous tile (250 g.; *ca.* 5 mm. diam.) in the minimum volume of water, and stirring in finely powdered aluminium phosphate (15 g.). The catalyst sludge was then introduced into the pyrolysis tube and dried *in situ* by heating it at 300°/10 mm. for 2 hours. A fresh charge of catalyst is necessary after about 150 g. of carbinol have been passed through the tube.

The emergent gases were condensed in air and water condensers, and the product was collected in a flask cooled in ice–salt. After separation of the water produced, the crude product was distilled, and the fraction, b. p. <65°/30 mm., was dried ($CaCl_2$) and fractionated to give ethynyl*cyclo*hexene (35 g.), a mobile liquid with an odour reminiscent of garlic, b. p. 60°/30 mm., $n_D^{19°}$ 1·494 ± 0·002 (Found: C, 90·2; H, 9·6. Calc. for C_8H_{10}: C, 90·5; H, 9·5%) (Merling, D.R.P. 280,226, gives b. p. 148—151°, $n_D^{20°}$ 1·4922; Carothers and Coffman, *J. Amer. Chem. Soc.*, 1932, **54**, 4071, give b. p. 40—43°/12 mm.; Mousseron and Julien, *Bull. Soc. chim.*, 1946, 241, give b. p. 145—146°, $n_D^{23°}$ 1·4669). Light absorption: see Table. On analysis by the method of Hill and Tyson (*J. Amer. Chem. Soc.*, 1928, **50**, 172) the hydrocarbon (0·412 and 0·409 g.) liberated nitric acid equivalent to 35·0 and 34·6 c.c. of 0·0968N-alkali, corresponding to 0·87 atom of acetylenic hydrogen. (That this method gives low values has been confirmed in other determinations; thus pure ethynyl*cyclo*hexanol gave a value of only 0·90 acetylenic hydrogen.) Active hydrogen (Zerewitinoff): The hydrocarbon (83 mg.) evolved 15·6 c.c. of methane at 18°/771 mm., equivalent to 0·87 atom of active hydrogen per molecule. Quantitative hydrogenation: The hydrocarbon (619 and 552 mg.) in methanol (10 c.c.) was shaken in hydrogen in the presence of platinic oxide catalyst until absorption ceased. Hydrogen absorbed at 17°/747 mm., 381 and 345 c.c., equivalent to an average value of 2·65 ⊢.

*Vinyl*cyclo*hexene.*—Ethynyl*cyclo*hexene (5·0 g.) in ethyl acetate (20 c.c.) was shaken in hydrogen in the presence of a palladium–calcium carbonate catalyst (0·5 g.; 0·3% Pd) until 950 c.c. of gas had been absorbed at 17°/763 mm. After removal of the catalyst by filtration through alumina, distillation gave vinyl*cyclo*hexene (2·2 g.), b. p. 145°, $n_D^{14°}$ 1·4911 (Cook and Lawrence, *J.*, 1938, 58, give b. p. 145°). The *p*-benzoquinone adduct crystallised from light petroleum (b. p. 40—60°) in pale yellow plates, m. p. 84—85° (Cook and Lawrence, *loc. cit.*, give m. p. 84—85·5°).

*Ozonolysis of Ethynyl*cyclo*hexene.*—Ozonised oxygen was slowly bubbled through a solution of the acetylene (1·0 g.) in glacial acetic acid (25 c.c.) at 0° for 10 hours. The ozonide was decomposed *in situ* by addition of hydrogen peroxide (20 c.c.; 50 vol.), and the solution evaporated under reduced pressure. Crystallisation of the residue from water gave adipic acid (0·3 g.), m. p. 146—147°, undepressed on admixture with an authentic specimen.

Crotonylideneacetone.—Crotonaldehyde (300 g.) was added dropwise during 4 hours to a well-stirred solution of acetone (600 g.) in aqueous sodium hydroxide (0·4%; 2000 c.c.) cooled to between 0° and 5°. After the addition of the aldehyde the mixture was stirred for a further 30 minutes, saturated with salt, acidified with 2N-sulphuric acid, and extracted with ether. After it had been washed to remove acid and dried, the ether was removed and the product distilled in steam. The distillate was extracted twice with ether, and the ethereal solution washed twice with a small volume of water, and dried. Distillation then gave crotonylideneacetone (42 g.), b. p. 63°/10 mm., $n_D^{18°}$ 1·5223—1·5227. Light absorption: Maximum, 2700 A.; ϵ = 28,500.

8-cyclo*Hex*-1′-*enyl*-6-*methylocta*-2 : 4-*dien*-7-*yn*-6-*ol* (VI).—Ethynyl*cyclo*hexene (62 g.) in dry ether (100 c.c.) was added dropwise to a solution of ethylmagnesium bromide (from 12·5 g. of magnesium) in ether (1000 c.c.), and after the addition was complete the mixture was heated under reflux for 3 hours. Crotonylideneacetone (55 g.; distilled in nitrogen immediately before use) in ether (600 c.c.) was then gradually added to the stirred Grignard reagent at 0—5° during 3 hours. After being stirred overnight

* *Added in Proof.*—By the methods envisaged above, the C_{14} lower homologue of (IX) has been prepared from (V) by employing sorbaldehyde in place of crotonylideneacetone (Heilbron, Jones, Lewis, Richardson, and Weedon, *J.*, in the press), and, also, mono- and di-methyl homologues of (IX) have been synthesised from 2-methyl- and 6 : 6-dimethyl-ethynyl*cyclo*hexene respectively (forthcoming publication).

at room temperature, the complex was decomposed with ice and ammonium chloride (250 g.), and the product was isolated *via* ether. Distillation in a short-path still gave 8-cyclo*hex*-1′-*enyl*-6-*methyl*-*octa*-2 : 4-*dien*-7-*yn*-6-*ol* (60 g.) as a pale yellow viscous liquid, b. p. 80—85° (bath temp.)/10^{-5} mm., $n_D^{16°}$ 1·5464 (Found: C, 83·25; H, 9·35. $C_{15}H_{20}O$ requires C, 83·25; H, 9·35%). Light absorption: see Table. Active hydrogen (Zerewitinoff): The carbinol (116 mg.) evolved 13·5 c.c. of methane at 19°/766 mm., equivalent to 1·05 atoms of active hydrogen per mol.

8-cyclo*Hex*-1′-*enyl*-6-*methylocta*-3 : 5-*die n*-7-*yn*-2-*ol* (VII).—The foregoing tertiary carbinol (55 g.) in ether (50 c.c.) was shaken for 15 hours with sulphuric acid (2500 c.c.; 0·5% w/v) and a trace of quinol. Isolation of the product gave the *carbinol* (40 g.) as an extremely viscous, pale yellow liquid, b. p. 100—110° (bath temp.)/10^{-5} mm., $n_D^{20°}$ 1·5790 (Found: C, 82·5; H, 9·65. $C_{15}H_{20}O$ requires C, 83·25; H, 9·35%). Light absorption: see Table. Active hydrogen (Zerewitinoff): The carbinol (105 mg.) evolved 12·8 c.c. of methane at 19°/766 mm., equivalent to 1·1 atoms of active hydrogen per mol. The 3 : 5-*dinitrobenzoate* crystallised from light petroleum (b. p. 60—80°) in small rosettes of bright yellow needles, m. p. 113° (Found: N, 6·8. $C_{22}H_{22}O_6N_2$ requires N, 6·85%).

8-cyclo*Hexyl*-6-*methyloctan*-2-*one*.—A solution of the above carbinol (VII; 2·83 g.) in methanol (50 c.c.) was shaken with hydrogen and platinic oxide catalyst until absorption was complete (1505 c.c. at 17°/755 mm., equivalent to 4·8 F). The catalyst was filtered off, and, after removal of the methanol, the saturated carbinol was oxidised with a solution of chromium trioxide in acetic acid. Isolation of the product and distillation gave 8-cyclo*hexyl*-6-*methyloctan*-2-*one* (2·45 g.), b. p. 85°/0·1 mm., $n_D^{19°}$ 1·4668 (Found: C, 79·9; H, 12·1. $C_{15}H_{28}O$ requires C, 80·3; H, 12·6%). The *semicarbazone* crystallised from aqueous methanol in glistening plates, m. p. 98° (Found: N, 14·85. $C_{16}H_{31}ON_3$ requires N, 14·95%).

8-cyclo*Hex*-1′-*enyl*-6-*methylocta*-3 : 5-*dien*-7-*yn*-2-*one* (VIII).—A solution of the rearranged carbinol (VII; 28·5 g.) and aluminium *tert.*-butoxide (50 g.) in dry acetone (1000 c.c.) and dry benzene (1500 c.c.) was refluxed for 50 hours. The cooled solution was poured into 2N-sulphuric acid (2000 c.c.), the mixture was quickly shaken to decompose the aluminium complex, and the organic layer was separated, washed with sodium hydrogen carbonate solution and water, and dried. Evaporation of the solvent and short-path high-vacuum distillation gave the crude ketone (25·5 g.), b. p. 80—100° (bath temp.)/10^{-5} mm., $n_D^{19°}$ 1·5994. Light absorption: Maxima, 2950 and 2360 A.; $E_{1\,cm.}^{1\%}$ 770 and 650 respectively. Inflexion, 3070 A.; $E_{1\,cm.}^{1\%}$ 650. This crude material was treated with semicarbazide acetate in aqueous methanol, and gave a product (17 g.), m. p. 187—188° after two crystallisations from methanol. Further recrystallisation from aqueous methanol gave the pure *semicarbazone* as needles, m. p. 194° (decomp.; rapid heating) (Found: N, 15·6. $C_{16}H_{31}ON_3$ requires N, 15·5%). Light absorption: Maximum, 3360 A.; $\epsilon = 46{,}500$. Inflexion, 3520 A.; $\epsilon = 26{,}000$.

The semicarbazone (17·5 g.; m.p. 187°) was refluxed with vigorous stirring with 2N-sulphuric acid (200 c.c.) and light petroleum (400 c.c.; b. p. 80—100°) until all the solid had disappeared. After isolation, high-vacuum distillation gave the *ketone* (12·7 g.) as a pale yellow viscous liquid, b. p. 80—85° (bath temp.)/10^{-5} mm., $n_D^{16°}$ 1·6185 (Found: C, 83·8; H, 8·4. $C_{16}H_{18}O$ requires C, 84·05; H, 8·5%). Light absorption: see Table.

Hydrogenation of the ketone in methanol, employing a platinic oxide catalyst, and treatment of the product with semicarbazide acetate gave the semicarbazone of 8-*cyclo*hexyl-6-methyloctan-2-one, m. p. 97—98°, undepressed on admixture with the specimen described above.

4-cyclo*Hex*-1′-*enylbut*-3-*yn*-2-*one* (X).—Ethynyl*cyclo*hexene (62 g.) in dry ether (100 c.c.) was added dropwise to an ethereal solution of ethylmagnesium chloride (from 12·25 g. of Mg), and the mixture was refluxed for 3 hours. After cooling, the cold ethereal suspension of the Grignard reagent was added slowly with stirring to a solution of acetic anhydride (102 g.) in dry ether (250 c.c.) at −60°. Stirring was continued while the temperature of the mixture was allowed to reach −5° during 4 hours; ice was then added, and the ethereal layer was washed free from acid and dried. Distillation gave 4-cyclo*hex*-1′-*enylbut*-3-*yn*-2-*one* (36 g.) as a pleasant smelling, mildly vesicant liquid, b. p. 70°/0·1 mm., $n_D^{17°}$ 1·5307 (Found: C, 80·7; H, 8·3. $C_{10}H_{12}O$ requires C, 81·0; H, 8·2%). Light absorption: Maxima, 2720 and 2200 A.; $\epsilon = 11{,}000$ and 6000 respectively. The *semicarbazone* crystallised from aqueous methanol in needles, m. p. 126° (Found: C, 64·65; H, 7·5. $C_{11}H_{15}ON_3$ requires C, 64·4; H, 7·4%). Light absorption: Maximum 2820 A.; inflexion 2280 A.; $\epsilon = 16{,}500$ and 15,500 respectively. The 2 : 4-*dinitrophenylhydrazone* crystallised from alcohol in silky orange or yellow needles, m. p. 146°, the yellow form reverting to the orange at *ca.* 130° (Found: C, 58·4; H, 4·75. $C_{16}H_{16}O_4N_4$ requires C, 58·5; H, 4·9%). Light absorption (main band only): Orange form, maximum 3700 A.; $\epsilon = 30{,}500$. Yellow form, maximum, 3700 A.; $\epsilon = 27{,}000$. The 2 : 4-*dinitrophenylsemicarbazone* crystallised from benzene in pale yellow needles, m. p. 157° (Found: C, 54·9; H, 4·8. $C_{17}H_{17}O_5N_5$ requires C, 54·95; H, 4·65%). Light absorption (in chloroform): Maxima 2690, 3080, and 3160 A.; $\epsilon = 14{,}000$, 14,000, and 14,000 respectively.

4-cyclo*Hexylbutan*-2-*one*.—A solution of the above ketone (2·0 g.) in ethyl acetate (15 c.c.) was shaken with hydrogen and platinic oxide catalyst until absorption ceased (985 c.c. at 20°/755 mm., equivalent to 3·3 F). After removal of the catalyst, distillation gave 4-cyclo*hexylbutan*-2-*one* (1·5 g.) as a pleasant smelling liquid, b. p. 108°/15 mm., $n_D^{20°}$ 1·4584 (Found: C, 77·9; H, 11·8. $C_{10}H_{18}O$ requires C, 77·9; H, 11·75%). The *semicarbazone* crystallised from aqueous methanol in needles, m. p. 163° (Found: C, 62·4; H, 9·8. $C_{11}H_{21}ON_3$ requires C, 62·5; H, 10·05%). The 2 : 4-*dinitrophenylhydrazone* formed small orange plates, m. p. 106°, from methanol (Found: C, 57·8; H, 6·9. $C_{16}H_{22}O_4N_4$ requires C, 57·45; H, 6·65%). Oxidation of the ketone with hypobromite gave a crude acid, the amide of which when crystallised from aqueous methanol had m. p. 118° (Zelinsky, *Ber.*, 1908, **41**, 2677, gives m. p. 120° for β-*cyclo*hexylpropionamide).

6-cyclo*Hex*-1′-*enyl*-4-*methylhexa*-1 : 3-*dien*-5-*yne*-1-*carboxylic Acid* (XI).—The above acetylenic ketone (50 g.), methyl ω-bromocrotonate (60 g.), activated zinc turnings (23 g.), and dry benzene (500 c.c.) were heated under reflux. After 10—15 minutes the solution darkened and a vigorous reaction set in (a crystal of iodine was usually effective in initiating the reaction when it proved reluctant to start);

external cooling was then immediately applied. Refluxing was continued for a further 30 minutes after the spontaneous reaction had subsided. The deep greenish-black solution was decanted from unreacted zinc, and treated with ice-cold acetic acid (600 c.c.; 10%). The benzene layer was washed free from acid, dried, and evaporated, and distillation of the residue in a short-path still in high vacuum gave the crude hydroxy-ester (30·5 g.), b. p. 100—150° (bath temp.)/10^{-5} mm., $n_D^{17°}$ 1·525. Light absorption: Maximum, 2290 A.; $E_{1\,cm.}^{1\%}$ 700.

The crude ester was heated with anhydrous oxalic acid (75 g.) at 90—95°/10 mm. for 6 hours, and, after cooling, the product was extracted with light petroleum (b. p. 40—60°). The material (15·5 g.) obtained after distillation, b. p. 75—125° (bath temp.)/10^{-4} mm., $n_D^{18°}$ 1·556, contained an appreciable amount of dehydrated ester. Light absorption: Maxima, 3120, 2800, and 2290 A.; $E_{1\,cm.}^{1\%}$ 360, 360, and 500 respectively.

The crude esters (15·3 g.) were dissolved in a solution of potassium hydroxide in methanol (115 c.c.; 10%), and the mixture was kept at 20° for 20 hours and then poured on crushed ice (500 g.). After extraction of the non-saponifiable portion with ether, the acid was liberated from the aqueous solution by acidification to pH 3 with phosphoric acid, and isolated by means of ether. The resulting orange-red gum (6·4 g.), which solidified partially, was triturated with 70% aqueous methanol to give a crude solid acid (4·1 g.). Crystallisation from light petroleum (b. p. 60—80°) yielded 6-cyclo*hex*-1′-*enyl*-4-*methylhexa*-1 : 3-*dien*-5-*yne*-1-*carboxylic acid* (3·2 g.) as pale yellow needles, m. p. 137°, decomposing rapidly in contact with air (Found: C, 77·55; H, 7·45. $C_{14}H_{16}O_2$ requires C, 77·7; H, 7·45%). Light absorption: see Table. Active hydrogen (Zerewitinoff): The acid (75 mg.) evolved 8·2 c.c. of methane at 27°/765 mm., equivalent to 0·95 atom of active hydrogen per mol. Quantitative hydrogenation: The acid (148 mg.) in ethyl acetate (20 c.c.) was shaken with hydrogen and platinic oxide catalyst until absorption ceased. Hydrogen absorbed at 23°/765 mm., 81 c.c., equivalent to 4·9 F.

8-cyclo*Hex*-1′-*enyl*-6-*methylocta*-3 : 5-*dien*-7-*yn*-2-*one* (VIII).—To a solution of the above acid (6·0 g.; 1 mol.) in dry ether was added slowly with shaking a solution of methyl-lithium (2·5 mols.) in ether (50 c.c.). The solution was then heated under reflux for 5 minutes, cooled, and treated with ice–water (100 c.c.). The crude ketone, after isolation, was dissolved in an aqueous methanolic solution of semicarbazide acetate, and yielded 5·8 g. of the semicarbazone of the ketone (VIII), m. p. 192° (decomp.) (undepressed on admixture with the specimen prepared by the alternative route), exhibiting light absorption properties identical with those previously recorded.

8-cyclo*Hex*-1′-*enyl*-2 : 6-*dimethylocta*-1 : 3 : 5-*trien*-7-*yne*-1-*carboxylic Acids. The Isomeric* C_{17} *Acids* (IX).—A mixture of the regenerated ketone (VIII; 8·5 g.), freshly distilled methyl bromoacetate (6·1 g.), activated zinc turnings (2·6 g.), and dry thiophen-free benzene (500 c.c.), together with a crystal of iodine, was heated under reflux for 1 hour. The deep red mixture was then cooled, decanted from unreacted zinc, and shaken with N-acetic acid (200 c.c.). The benzene layer was washed free from acid, dried, and evaporated, giving a mixture of hydroxy- and unsaturated esters, mainly the former, $n_D^{14°}$ 1·585. Light absorption: Maxima, 3390, 3070, and 2190 A.; $E_{1\,cm.}^{1\%}$ 225, 640, and 770 respectively.

The ester mixture was dissolved in dry ether, the solution was poured on anhydrous oxalic acid (45 g.), and the ether was removed under diminished pressure. The residue was then heated at 95—100°/0·1 mm. for 3 hours, cooled, and extracted with light petroleum (b. p. 60—80°). The extract was washed and dried, and removal of the solvent under reduced pressure gave the unsaturated ester (10·6 g.), $n_D^{12°}$ 1·631. Light absorption: Maxima, 3420 and 2510 A.; $E_{1\,cm.}^{1\%}$ 1000 and 430 respectively.

The ester was dissolved in a solution of potassium hydroxide in methanol (250 c.c.; 10% w/v), and kept at 20° for 100 hours. Water (750 c.c.) was then added, the non-saponifiable material was extracted with ether, and the aqueous layer was acidified to pH 4 with phosphoric acid. The liberated acid was taken up into ether, and the solution was washed and dried. On concentration of the ethereal solution, *acid A* separated; it crystallised from ether as pale yellow iridescent needles (1·3 g.), m. p. 179° (Found: C, 79·5; H, 7·7. $C_{17}H_{20}O_2$ requires C, 79·65; H, 7·9%). Light absorption: see Table.

The solid obtained by evaporating the mother liquors, when crystallised from methanol, yielded a further amount (0·6 g.) of acid A, m. p. 175—176°. By diluting these mother liquors with water and keeping them at −5°, *acid B* was obtained, after crystallisation from methanol, as pale yellow needles (0·8 g.), m. p. 153° (Found: C, 79·25; H, 7·7. $C_{17}H_{20}O_2$ requires C, 79·65; H, 7·9%). Light absorption: see Table.

The authors thank the Rockefeller Foundation, and one of them (R. W. R.) thanks the Directors of Courtaulds, Ltd. (Textile Division), for financial assistance. Light-absorption data were determined by Dr. E. A. Braude. The authors are indebted to both F. Hoffmann–La Roche and Co., Ltd. (Basle), and Glaxo Laboratories, Ltd., for independent biological assays.

IMPERIAL COLLEGE OF SCIENCE AND TECHNOLOGY, LONDON, S.W.7. [*Received, May 5th,* 1948.]

69. *The Kinetics of Halogen Substitution. Part V. Halogen Addition. Part XIV. Catalysis by Electrolytes in Acetic Acid Solution.*

By P. W. Robertson, (the late) R. M. Dixon, W. G. M. Goodwin, I. R. McDonald, and J. F. Scaife.

Measurements have been made of the catalysis of bromination by various electrolytes, such as $HClO_4$, $LiClO_4$, LiCl, LiBr, H_2SO_4, NaOAc, in acetic acid solution, of (*a*) *m*-xylene and β-bromostyrene; (*b*) allyl bromide and 3 : 4- and 2 : 6-dichlorostyrene; (*c*) ethyl acrylate, maleic acid, and sodium ethylenesulphonate. Three types of catalysis are differentiated: (*a*) for normal electrophilic substitution or addition, the effectiveness being $HClO_4 > H_2SO_4$ and $LiClO_4 > LiCl$; the catalysis is in the order of the conductivities, and has the nature of a salt (activity) effect; (*b*) for electrophilic addition when a $+T$, $-I$ group is joined to an ethylene carbon atom; $LiCl > LiClO_4$ and $LiCl > LiBr$; (*c*) when nucleophilic reactivity is possible by the action of a $-T$, $-I$ group; $LiCl > LiClO_4$ and $LiBr > LiCl$.

Catalysis of chlorine substitution and addition is slight. Iodine addition shows a relatively low catalysis by $LiClO_4$ and $HClO_4$, but a large catalysis by LiCl and LiBr.

It has been shown that perchloric acid may catalyse considerably halogen addition in acetic acid solution to unsaturated aldehydes (*J.*, 1945, 888), and likewise lithium chloride accelerates bromine addition to such compounds as allyl chloride and vinyl bromide (*J.*, 1945, 131; 1947, 630). Perchloric acid and lithium chloride may also act as catalysts, although less efficiently, in halogenation reactions which have the normal electrophilic character, *e.g.*, in the bromination of mesitylene, or in bromine addition to such ethylene derivatives as β-bromostyrene. As acetic acid is a solvent of low dielectric power, and since the ionisation of a halogen atom would appear to be a rate-determining process, it was suggested in our earlier communications that such catalysis might be of the nature of a salt effect, for according to Kolthoff and Willman (*J. Amer. Chem. Soc.*, 1934, **56**, 1007) perchloric acid and lithium chloride are electrolytes in acetic acid solution. Perchloric acid is a strong electrolyte compared, for example, with nitric acid, as its equivalent conductivity is 400 times greater than that of nitric acid at the same molar concentration, but on the other hand it is a weak electrolyte in the sense that in 0·01M-solution it is dissociated to the extent of less than 1%. That is equally true of lithium chloride, which has similarly a small degree of dissociation, and obeys the Ostwald dilution law over the concentration range examined by Kolthoff and Willman. In spite of the relatively small dissociation of lithium chloride, it appears to have an activity effect in the isomerism of α-phenylallyl acetate in acetic acid solution (for reference and discussion, see Catchpole and Hughes, *J.*, 1948, 3), whilst for lithium and potassium acetate the effect is considerably smaller. These results are consistent with the values for the molecular conductivities (quoted after Table I, p. 295), and correspondingly it will be shown that the catalytic efficiencies of lithium chloride and sodium acetate in the reactions now studied have a similar order.

Certain typical reactions have been examined in greater detail than previously, and the conductivities of perchloric acid and lithium chloride measured over a higher concentration range than that studied by Kolthoff and Willman. The results reveal that these solutions show minima in the molecular conductivities (at M/64 for perchloric acid, and M/32 for lithium chloride), indicating the formation of triple ions. In Fig. 1 are shown the results obtained for the bromination of *m*-xylene with different amounts of added perchloric acid.

In Fig. 2 are the results for the lithium chloride-catalysed addition of bromine to β-bromostyrene; included also in the diagram are the measurements at double the lower concentration, giving an order, $n = 3{\cdot}0$, for the uncatalysed reaction, and a corrected order, $n = 2{\cdot}3$, for the catalysed reaction. Inset are plotted (circles) the ratios of velocities of catalysed (corrected by subtraction of uncatalysed rate) and uncatalysed reactions against the concentrations of the electrolytes, whilst the broken curves show the specific conductivities of the solutions over this concentration range (the arrow indicates minimum molecular conductivity). With different amounts of catalyst for the same reaction, the catalytic activity is approximately proportional to the conductivity of the solutions. The deviation from linearity is in the reverse sense to that required if the electrolyte showed simple dissociation; but an exact proportionality between catalytic activity and conductivity is not necessarily to be expected, as the effects caused by single and triple ions may be somewhat different. Similar results were obtained for certain other reactions, chlorination of *m*-xylene ($HClO_4$), bromination of *m*-xylene (LiCl), and bromine addition to bromostyrene ($HClO_4$).

Table I summarises the relative efficiency of different catalysts in such reactions, as ratio of rates of corrected catalysed to uncatalysed reactions, the halogen being at M/80- and the catalyst at M/20-concentration.

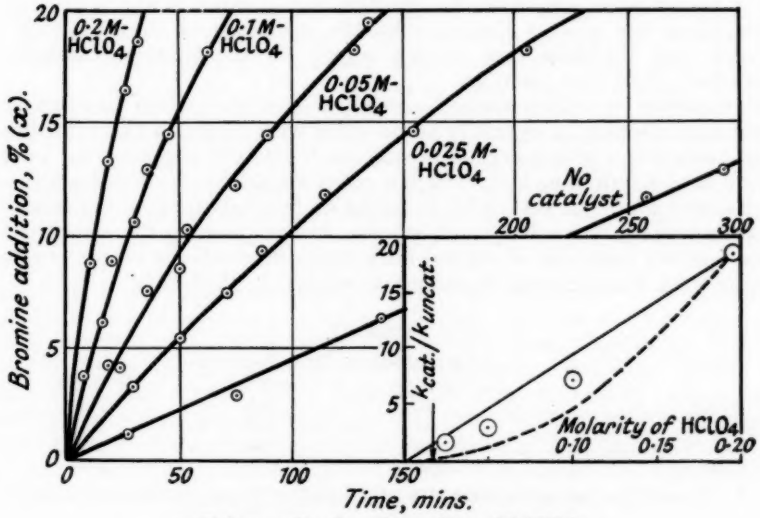
TABLE I.

	m-Xylene and chlorine.	*m*-Xylene and bromine.	Bromostyrene and bromine.	Undecenoic acid and iodine.
$HClO_4$	0·9	3·1	1·3	1·4
$LiClO_4$	—	—	1·3	1·5
LiCl	0·25	1·0	0·5	7·4
H_2SO_4	—	0·3	0·2	0·3
NaOAc	—	0·2	0·1	—

The molecular conductivities of the electrolytes, M/20, in acetic acid at 25° are as follows :

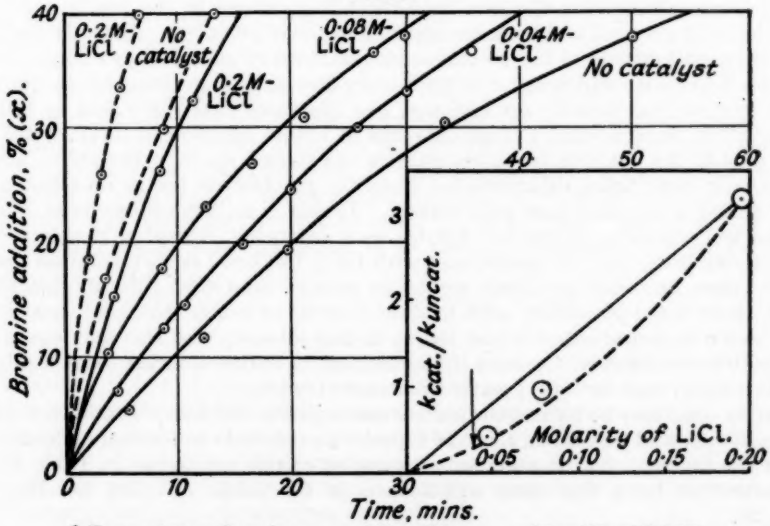
$HClO_4$.	$LiClO_4$.	LiCl.	NaOAc.	H_2SO_4.
1·50	0·81	0·23	0·18	0·09

FIG. 1.



m-*Xylene*, M/8 ; *bromine*, M/80, *with* $HClO_4$.

FIG. 2.



β-*Bromostyrene–bromine* : — M/10, M/80 ; - - - M/5, M/40 *with* LiCl.

It is apparent that there is a general relationship between the molecular conductivity and the catalytic activity, more especially when pairs of related electrolytes, *e.g.*, $LiClO_4$ and LiCl,

$HClO_4$ and H_2SO_4, are considered. The parallelism between the two types of reaction, the catalytic efficiency for bromine substitution being approximately double that for bromine addition, indicates that a similar mechanism is in operation, and this is regarded as a salt (activity) effect. In the presence of such a catalyst as lithium chloride, however, it has been found (with stilbene, M/80 + Br_2, M/80 + LiCl, M/4) that the reaction product contains not only the dibromo-, but also a large amount of the chlorobromo-compound, with some bromoacetate also. It is therefore evident that the chloride ion is effective in completing the second stage of the reaction, and if the catalysis is an activity effect, this second stage does not appear to be rate-determining. When the chloride ion does appear to take part in a rate-determining step (compounds in Table II), then the catalytic activities of lithium perchlorate and chloride become reversed, *i.e.*, are no longer in the order of their conductivities. The activity effect would seem, in both substitution and addition, to involve the stretching of the Br–Br link in the intermediate, with the resultant anionisation of one of the bromine atoms. But in substitution the process also includes the stretching of the C–H link with proton formation, and this difference may be the reason for the superior catalytic activity of electrolytes in the substitution reaction.

The weak catalysis by sodium acetate, possibly related to the fact that this compound is a base in acetic acid solution, is especially to be noted with regard to the substitution reaction. Since sodium acetate is a proton-acceptor, such small catalysis suggests that the removal of a proton is not a rate-determining step. Such a result should be contrasted with the conclusion reached by Bennett *et al.* (*J.*, 1947, 474) for nitration in sulphuric acid solution. In nitration the electrophilic reagent is the NO_2^+ ion, whereas in halogenation the attack is by a neutral molecule, the reaction being one of mutual interchange in which the proton removal is part of the actual process (cf. Hinshelwood, Presidential Address, *J.*, 1947, 694).

TABLE II.

	3 : 4-Dichloro-styrene.	2 : 6-Dichloro-styrene.	Allyl bromide.
$HClO_4$	—	1·3	1·3
$LiClO_4$	—	1·3	1·3
LiCl	1·7	2·0	4·0
LiBr *	0·9	1·5	2·8

* These values are not corrected for the small (unknown) uncatalysed rate.

On comparing different halogens, it is seen that the relative catalysis is less for chlorine than for bromine, and this may be related to the superior ionising power of the chlorine. But the comparison is complicated by the fact that there is a change in the reaction order, chlorine addition being of the second and bromine addition of the third order. Actually the difference in effect would be still greater if the second-order reactions of each halogen could be compared. Both bromine and iodine addition are of third order under the experimental conditions, and it is found that lithium perchlorate, for instance, has the same catalytic effect in each reaction; there is, however, an abnormally large catalysis of iodine addition by lithium chloride. One possibility is that the chloride ion takes part in the second stage of the iodine addition by a rate-determining step, being differentiated from the perchlorate ion in its effect owing to its power of forming a covalent link with carbon. If this is so, lithium bromide, which is more ionised than the chloride, should be superior as a catalyst. Actually, it shows considerable catalytic activity (ratio, 6·9, in comparison with LiCl, 7·4) but $LiBrI_2$ formation would tend to reduce this value, and such an effect would be greater than with lithium chloride. On the other hand, there is the possibility with lithium chloride of iodine chloride formation (as in the reaction between mercuric chloride and iodine in this solvent), and this may cause in part the catalysis by lithium chloride, for even if the amount of iodine chloride formed might be very small, it has a high reactivity (10^5 greater than that of iodine).

Whereas, in what may be termed the normal electrophilic addition of bromine, the electrolytes lithium perchlorate and perchloric acid are superior as catalysts to lithium chloride, for certain compounds the reverse effect is observed; examples of this are shown in Table II, where the catalytic activities have the same significance as for Table I, being for Br_2, M/80, and catalyst, M/20.

The compounds in Table II are of the type, $CHR'{:}CH_2$, where R′ is a group of opposing electronic requirement. This is shown for instance by bromomethyl, which is chiefly *o*,*p*-directing, with a small *m*-directing power. In the 3 : 4-dichlorophenyl group, the introduction of the two chlorine atoms reduces the rate of bromine addition by a factor of 200,

so that here also the tautomeric effect which favours the addition is offset by an inductive effect. The 2 : 6-dichlorophenyl group is similar, although with this compound there is the possibility of steric hindrance also (the rate of 2 : 6-dichlorostyrene being less than that of styrene by a factor of 10^4). Vinyl bromide would also be included in this class, and special mechanisms involving an initial attack by chloride ions were proposed to explain the abnormally high catalysis by lithium chloride of bromine addition to the allyl halides and vinyl bromide (*loc. cit.*). An alternative mechanism, however, is also possible, namely, an initial electrophilic attack by halogen, followed by a rate-determining stage in which the addition of the chloride ion to the intermediate, $\overset{+}{C}HR'-CH_2-\overset{-}{Br}-Br$, is aided by the withdrawal of electrons by the group R'. Whereas the catalysis with lithium chloride becomes greater for this type of compound, the efficiency of perchloric acid and lithium perchlorate does not increase. Such a specific effect for the chloride ion is attributed to the fact that it can form a covalent link with the carbon atom to which it becomes attached, whereas this is not possible for the perchlorate ion. Equally the bromide ion can form a covalent link, and lithium bromide should be expected to be more efficient than the chloride (molecular conductivities, LiCl, 0·23; LiBr, 0·45) but its effect is offset by the removal of bromine as $LiBr_3$. It is to be noted that the lithium bromide catalysis increases in the same order as for lithium chloride (Table II).

Another class of compound is characterised by showing a considerable catalysis of bromine addition by lithium chloride, and a still larger catalysis by the bromide, whilst the effect with the perchlorate remains relatively small. The catalytic ratios for certain of these compounds (bromine at M/80 and 4 mols. of catalyst, except for maleic acid, where these amounts are doubled) are shown in Table III; with the first two compounds, sodium acetate is present to prevent acid catalysis.

We have shown, in previous communications, that the addition of bromine to acrylic and maleic acids in acetic acid solution is greatly catalysed by hydrogen bromide, and we have produced evidence, mainly from the effect of constitution of the olefin on the rate of reaction, that such additions proceed by a nucleophilic mechanism. We have further shown that hydrogen chloride is also a catalyst for bromine addition to related compounds, *e.g.*, the 1 : 2-unsaturated aldehydes, and although considerably less effective than hydrogen bromide, it is more efficient than would be expected from a comparison with certain other acids, which are more ionised in the solvent, acetic acid. The evidence indicated that the reagents in these reactions were HBr_3 and $HClBr_2$, and similarly for ethyl acrylate and maleic acid (Table III) it is

TABLE III.

	CH_2:CH·CO_2Et.	CH(CO_2H):CH·CO_2H.	CH_2:CH·SO_3Na.
$LiClO_4$	0·8	0·2	0·7
LiCl	10	6	6·7
LiBr	33	30	—

concluded that the catalysis is due to $LiBr_3$ and $LiClBr_2$, or more particularly to Br_3^- and $ClBr_2^-$ ions, as lithium bromide and lithium chloride themselves are appreciably dissociated in acetic acid solution. There is also evidence, of a constitutional nature, that these reactions are nucleophilic in character : thus the rate of bromine addition to maleic acid in the presence of lithium chloride is 8 times faster than to citraconic acid, whereas in aqueous acetic acid, *i.e.*, under electrophilic conditions, this order is reversed (*J.*, 1945, 129). With regard to the actual formulation of such nucleophilic reactions, it is not yet established whether the organic

$\overset{\oplus}{C}H_2-CH=C(OEt)-\overset{\ominus}{O}$ (I.)

$\overset{\oplus}{C}H_2-CH=C(OEt)-\overset{\leftarrow\ominus}{O}\ldots H\ldots\overset{\leftarrow\ominus}{O}Ac$ (II.)

compound reacts according to a resonance structure (I), or whether solvent molecules are required to establish, by a hydrogen bond, the positive charge on the β-carbon atom (II).

The corresponding catalytic ratios of lithium chloride for chlorine addition have also been measured, *viz.*, ethyl acrylate (~0·1), maleic acid (0·35). The catalysis tends to be small, as for chlorine substitution (Table I). The larger effect for maleic acid is attributed to the influence of the electron-attracting carboxyl group on the β-carbon atom in aiding the second stage of the electrophilic substitution (as for compounds in Table II).

Sodium ethylenesulphonate (Table III) similarly shows a large lithium chloride catalysis, even although the uncatalysed (electrophilic) rate is relatively high owing to the ionisation of the compound. Ethylenesulphonic acid itself, whilst not showing acid catalysis of bromine addition with perchloric acid, gives a large catalysis with hydrogen bromide. Compounds with

the SO_2R group, therefore, appear also capable of nucleophilic reactivity, and the initial attack in the catalysis of sodium ethylenesulphonate could therefore be expressed by $ClBr_2^- \curvearrowright CH_2^+—CH=SO_2^-\cdot ONa$.

The results obtained in the present investigation for the catalysis of bromine addition by electrolytes in acetic acid solution reveal that unsaturated compounds are divisible into three classes, which may be specified, with reference to the nomenclature proposed by Ingold (cf. Ingold and Ingold, *J.*, 1931, 2354), as follows :

Class I. Compounds of the types $CHR:CH_2$ and $CHR:CHX$ (the arrows indicating the point of electrophilic attack), where R is a group ($+I$ or $+T$), and X a halogen atom or group such as chloromethyl ($-I$), or a group such as phenyl which in this position may exert a relatively weak tautomeric effect ($-T$). Actually, compounds, $CHR:CH_2$, where R is phenyl or an alkyl, are too reactive for convenient measurement, but allyl esters, $CH(CH_2\cdot O\cdot COR):CH_2$, approximate to this type. The relative catalysis is $LiClO_4 > LiCl$, being in the order of their molecular conductivities, and is apparently chiefly a salt (activity) effect; further $LiCl > LiBr$.

Class II. Compounds of the type $CHR':CH_2$, where R' is a group of opposing electronic requirements, such as bromomethyl ($+T$, $-I$). The relative efficiency is $LiCl > LiClO_4$, as the chloride ion becomes involved in a rate-determining step of the reaction; here also $LiCl > LiBr$.

Class III. Compounds of the type $CH_2:CHX$, where X is a group like carboxyl ($-T$, $-I$). The catalysed reactions now proceed by a nucleophilic mechanism, and the active reagent in catalysis by lithium chloride is the $ClBr_2^-$ ion. The effect here may be considerable, whereas the lithium perchlorate catalysis remains small, as for Classes I and II. The relative efficiency is $LiCl > LiClO_4$, and $LiBr > LiCl$. This class would also include compounds of the type $CHX:CHX$ (*e.g.*, maleic acid), as well as compounds, $CHR:CHX$ (when X is a strong $-T$ group). The compound $CHPh:CH\cdot NO_2$ was selected as a representative example; considerable lithium chloride catalysis was established (in presence of sodium acetate), but the exact catalytic ratio could not be determined as the uncatalysed reaction appeared to be accompanied by polymerisation.

Experimental.

The technique and materials were as previously described. In addition there were used ethyl acrylate, b. p. 95·5—96·5°/725 mm., and 2 : 6- and 3 : 4-dichlorostyrene. For the last two substances we are indebted to the kindness of Dr. C. S. Marvel, University of Illinois; the compounds were distilled under reduced pressure before measurement, and showed the theoretical bromine absorption. The solutions of catalysts were prepared as previously described. In addition, standard lithium perchlorate was prepared by mixing equal volumes of equimolecular lithium chloride and perchloric acid solutions; hydrogen chloride was freely evolved and dry nitrogen was bubbled through the solution until it gave a negative test for chloride. Catalytic ratios for sodium ethylenesulphonate are quoted in Table III, and more detailed results for the rates, etc., of this compound will be given in a later communication. Herewith details of a typical experiment.

M/10-*β*-*Bromostyrene* + M/80-*bromine* + M/25-LiCl *in acetic acid at* 24°. Reaction mixture 10 ml.; 1 ml. titrated with N/80-$Na_2S_2O_3$.

Time, mins.	0	4	10·5	20	30	44	60
Titre	1·97	1·83	1·64	1·43	1·27	1·10	0·96

From curve : $x = 20$, $t = 14·3$. Second expt. : $x = 20$, $t = 14·3$.

There follows a summary of further results quoted as times (t), in mins., for % halogen absorption, for dark reactions in acetic acid at 24°. *m*-Xylene, M/80, + Cl_2, M/80, $x = 20$, $t = 1·80$; +LiCl, M/10, $t = 1·20$; +$HClO_4$, M/20, $t = 0·94$. *m*-Xylene, M/8, +Br_2, M/80, $x = 10$, $t = 225$; +LiCl, M/20, $t = 110$; +$HClO_4$, M/20, $t = 54$; +NaOAc, M/10, $t = 160$. (In the sodium acetate catalysis, interference from liberated hydrogen bromide is negligible, as from $x = 0$ to $x = 10$, [NaOAc]/[HBr] = 160, and from experiments with added hydrogen bromide the effect of an equal amount of this is very small.) *β*-Bromostyrene, M/8, + Br_2, M/80, $x = 20$, $t = 17$; +$HClO_4$, M/20, $t = 7·5$; +H_2SO_4, M/10, $t = 11·2$. *β*-Bromostyrene, M/10, +Br_2, M/80, $x = 20$, $t = 20·5$; +LiCl, M/20, $t = 13·5$; +$LiClO_4$, M/20, $t = 9·5$; +$HClO_4$, M/20, $t = 9·5$. Undecenoic acid, 0·47M, +I_2, 0·0125M, $x = 10$, $t = 6·5$; +$HClO_4$, M/10, $t = 1·7$; +LiCl, M/40, $t = 2·0$; +H_2SO_4, M/10, $t = 4·0$. Undecenoic acid, 0·23M, +I_2, 0·0125M, $x = 10$, $t = 11·5$; +LiCl, M/20, $t = 1·4$; +$LiClO_4$, M/20, $t = 4·6$; +$HClO_4$, M/20, $t = 5·2$. 2 : 6-Dichlorostyrene, M/80, +Br_2, M/80, $x = 10$, $t = 11·5$; +LiCl, M/20, $t = 3·7$; +LiBr, M/20, $t = 6·5$; $LiClO_4$, M/20, $t = 4·9$; +$HClO_4$, M/20, $t = 4·9$. 3 : 4-Dichlorostyrene, M/80, +Br_2, M/80, $x = 50$, $t = 1·95$; +LiCl, M/10, $t = 0·45$, +LiBr, M/10, $t = 2·15$. Allyl bromide, M/80, +Br_2, M/80, $x = 20$, $t = 19·0$; +LiCl, M/20, $t = 3·9$; +LiBr, M/20, $t = 6·8$; +$LiClO_4$, M/20, $t = 8·5$; +$HClO_4$, M/20, $t = 8·5$. Ethyl acrylate, M/5, +Cl_2, M/80, +NaOAc, M/80, $x = 20$, $t = 42$; +LiCl, M/5, $t = 30$. Ethyl acrylate, M/80, +Br_2, M/80, $x = 20$, $t = 5160$; +$LiClO_4$, M/20, $t = 2760$; +LiCl, M/20, $t = 480$; +LiBr, M/20, $t = 150$. Maleic acid, M/5, +Cl_2, M/80, +NaOAc, M/80, $x = 5$, $t = 2400$; +LiCl, M/5,

$t = 1{,}000$. Maleic acid, M/10, $+Br_2$, M/40, +NaOAc, M/40, $x = 20$, $t = 3{,}000$; $+NaClO_4$, M/10, $t = 2{,}500$; +LiCl, M/10, $t = 430$; +LiBr, M/10, $t = 100$.

The ratios quoted in the tables are for the corrected catalysed rates to the uncatalysed rates, calculated for the most part at $x = 10$ or 20% halogen absorption; the ratios diverge slightly from these results as x increases. The catalytic ratios quoted in previous communications are given the same significance by the subtraction of unity.

The conductivities of perchloric acid and lithium chloride, represented in Figs. 1 and 2, are from measurements by Mr. W. S. Metcalf, of Victoria University College, and a further account will be given in a separate communication. We express our thanks to him, and to Dr. P. B. D. de la Mare, University College, London, for helpful discussion at various stages of the present investigation.

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[*Received, February 5th*, 1948.]

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70. *Trityl Derivatives of* D-*Arabofuranose.*

By G. J. HALLIBURTON and R. J. MCILROY.

Tritylation of methyl-D-arabofuranoside ($\alpha\beta$-mixture) with trityl chloride in pyridine gave crystalline 3 : 5-ditrityl methyl-D-arabofuranoside and trityl methyl-D-arabinoside as a syrup.

SMITH (*J.*, 1939, 753) prepared 5-trityl methyl-L-arabofuranoside by allowing methyl-L-arabofuranoside (1 mol.) to react with trityl chloride (0·95 mol.) in pyridine for 5 days at 20°. The compound was obtained as a glass in almost quantitative yield. The location of the trityl group on C_5 was established by methylation followed by detritylation and hydrolysis to give 2 : 3-dimethyl L-arabinose. Zeile and Kruckenberg (*Ber.*, 1942, **75**, 1127) prepared a ditrityl L-arabinose (m. p. 93°, optically inactive) by treating L-arabinose (1 mol.) with trityl chloride (2 mols.) in pyridine. Diacetyl and dibenzoyl derivatives of the ditrityl compound were prepared, but the location of the trityl groups was not established.

In the present investigation methyl-D-arabofuranoside ($\alpha\beta$-mixture) (1 mol.) was treated with trityl chloride (2 mols.) in pyridine for 12 hours at room temperature, followed by 1 hour on a boiling water-bath. 3 : 5-*Ditrityl methyl*-D-*arabofuranoside* was isolated, and identified by methylation to 3 : 5-*ditrityl* 2-*methyl methyl*-D-*arabofuranoside* which on detritylation and hydrolysis gave 2-methyl D-arabinose. Acetylation of the mother liquor after removal of the ditrityl compound yielded *diacetyl trityl methyl*-D-*arabinoside* as an orange glass.

Thus methyl-D-arabofuranoside and methyl-D-xylofuranoside behave similarly on tritylation, the latter yielding crystalline 3 : 5-ditrityl methylxylofuranoside and 5-trityl methylxylofuranoside as a syrup under the same conditions of tritylation (McIlroy, *J.*, 1946, 100).

EXPERIMENTAL.

D-*Arabinose.*—Calcium D-gluconate (120 g.) prepared from D-glucose by electrolytic oxidation (Isbell, Frush, and Bates, *Ind. Eng. Chem.*, 1932, **24**, 375) was converted into D-arabinose by a modification of Ruff's method (Hockett and Hudson, *J. Amer. Chem. Soc.*, 1934, **56**, 1632). The product (40 g.) had m. p. 155°, $[\alpha]_D^{18°}$ — 103° (*c*, 1·5 in water). Hockett and Hudson (*loc. cit.*) give m. p. 155·5—156·5°, $[\alpha]_D^{17°}$ — 103·3° (in water).

Methyl-D-*arabofuranoside.*—Anhydrous D-arabinose (20 g.) was dissolved in methanolic hydrogen chloride (400 c.c., 1%) at room temperature. The solution became non-reducing after 5 hours; $[\alpha]_D^{18°}$ — 66·8° (30 min.), — 35° (3 hrs.), — 32° (4 hrs.), + 40° (16 hrs.), + 43·6° (17 hrs.), + 42° (17½ hrs.), + 40° (18 hrs.). After neutralisation with silver carbonate, the filtrate was evaporated at 40° to a syrup which was then extracted thoroughly with ethyl acetate. Evaporation of the combined extracts gave a hygroscopic yellow syrup (2·0 g.), b. p. 160°/0·025 mm., $[\alpha]_D^{17°}$ + 64·5° (*c*, 0·6 in methyl alcohol) (Found: OMe, 16·8. Calc. for $C_6H_{12}O_5$: OMe, 18·9%). Baker and Haworth (*J.*, 1925, **127**, 365) give $[\alpha]_D$ + 71·3° (*c*, 0·8 in methyl alcohol) for methyl-D-arabofuranoside, a syrup. Montgomery and Hudson (*J. Amer. Chem. Soc.*, 1937, **59**, 992) report $[\alpha]_D$ + 100—105° for α-methyl-D-arabofuranoside. The rotation of the β-form is not recorded. The portion insoluble in ethyl acetate had $[\alpha]_D^{17°}$ — 101° (*c*, 1·0 in water), and was presumed to be $\alpha\beta$-methyl-D-arabopyranoside (Found: OMe, 18·4. Calc. for $C_6H_{12}O_5$: OMe, 18·9%). Hudson (*J. Amer. Chem. Soc.*, 1925, **47**, 265) gives $[\alpha]_D$ — 17° (in water) for α-methyl-D-arabopyranoside, while Purdie and Rose (*J.*, 1906, **89**, 1204) give $[\alpha]_D$ — 245° (in water) for β-methyl-D-arabopyranoside.

Tritylation of Methyl-D-*arabofuranoside.*—Methyl-D-arabofuranoside ($\alpha\beta$-mixture) (1·4 g.) was dissolved in dry pyridine (15 c.c., b. p. 116°). Dry trityl chloride (4 g.) was added, and the solution, after standing for 12 hours at room temperature, was heated for 1 hour with exclusion of moisture on a boiling water-bath. To the solution at 0° distilled water was added to permanent turbidity, and the solution then poured into ice–water (700 c.c.). After 3 hours the separated red gum was washed with water by decantation and dissolved in ether, and the ether solution washed with dilute acetic acid, aqueous sodium hydrogen carbonate, and finally with water. The ether extract, dried (Na_2SO_4) and evaporated under reduced pressure, yielded a red syrup which, from solution in chloroform, deposited colourless crystals (3·4 g.) of *ditrityl methyl*-D-*arabofuranoside*, m. p. 148—149°, $[\alpha]_D^{17°}$ + 11·9° (*c*, 1·95 in chloroform) (Found: trityl, 74·99; OMe, 4·6. $C_{44}H_{40}O_5$ requires trityl, 74·90; OMe, 4·78%).

Diacetyl Trityl Methyl-D-arabofuranoside.—The mother liquor, which did not crystallise after several weeks, was dissolved in dry pyridine (10 c.c.), and acetic anhydride (12 c.c.) added. After standing at 0° for 24 hours, the solution was poured into ice–water (500 c.c.). The creamy gum which separated was washed with water by decantation and dissolved in ether, and the ether solution washed with aqueous sodium hydrogen carbonate until acid-free and then with water. The ether extract, dried (Na_2SO_4) and evaporated under reduced pressure, yielded *diacetyl trityl methyl-D-arabinoside* (0·7 g.) as an orange glass, $[\alpha]_D^{18°}$ + 27·2° (*c*, 0·55 in chloroform) (Found: trityl, 49·1; acetyl, 17·6; OMe, 6·3. $C_{29}H_{30}O_7$ requires trityl, 49·6; acetyl, 17·6; OMe, 6·3%).

3 : 5-*Ditrityl 2-Methyl Methyl-D-arabofuranoside.*—Ditrityl methyl-D-arabofuranoside (3·3 g.) dissolved in methyl iodide (15 c.c.) was refluxed for 8 hours at 45°, silver oxide (10 g.) being added in 1 g. portions at hourly intervals. The methylated *product* was extracted with chloroform and the solvent evaporated under reduced pressure, yielding colourless crystals (3·4 g.), m. p. 107—108°, $[\alpha]_D^{18°}$ + 23·1° (*c*, 0·65 in methyl alcohol) (Found: OMe, 9·0. $C_{45}H_{42}O_5$ requires OMe, 9·4%).

Detritylation of Ditrityl Methyl Methyl-D-arabofuranoside.—Ditrityl methyl methyl-D-arabofuranoside (3·2 g.) was dissolved in dry chloroform (25 c.c.), and the solution saturated at 0° with hydrogen chloride. After standing for 1 hour at 0° and 1 hour at 20° the chloroform solution was exhaustively extracted with warm water. The combined aqueous extracts were neutralised with silver carbonate, and the filtrate evaporated at 40° under reduced pressure to a thick syrup which was converted into the glycoside by refluxing it with methanolic hydrogen chloride (50 c.c., 1%) for 6 hours. Hydrogen chloride was removed by silver carbonate, and the filtrate, evaporated under reduced pressure, yielded colourless crystals (0·62 g.), m. p. 44—45° (from ether), $[\alpha]_D^{17°}$ − 205° (*c*, 1·6 in methyl alcohol). Drying in a vacuum for 12 hours raised the m. p. to 62—63°. Oldham and Honeyman (*J.*, 1946, 986) give m. p. 46—47°, raised to 63—65° on vacuum drying, $[\alpha]_D^{18°}$ + 208° (in methyl alcohol), for 2-methyl β-methyl-L-arabinoside. The elevation of the m. p. on vacuum drying is attributed to dehydration of the monohydrate (Found: OMe, 35·0. Calc. for $C_7H_{14}O_5$: OMe, 34·8%).

2-*Methyl Arabinose.*—2-Methyl β-methyl-D-arabinoside (0·6 g.) was hydrolysed by aqueous sulphuric acid (60 c.c., 3%) during 3 hours at 95°. After neutralisation with barium carbonate, filtration, and evaporation, the residue was extracted with ether and boiling methyl alcohol. Evaporation of the combined extracts yielded a thick syrup (0·46 g.), $[\alpha]_D^{18°}$ − 102° (*c*, 1·5 in water) (Found: OMe, 18·7. Calc. for $C_6H_{12}O_5$: OMe, 18·9%). Schmidt and Simon (*J. pr. Chem.*, 1939, **152**, 190) give $[\alpha]_D^{20°}$ − 102° ± 3° (in water) for 2-methyl D-arabinose. The product, on treatment with phenylhydrazine, gave arabinosazone, m. p. 154·5—155° (decomp.), not depressed by authentic arabinosazone, m. p. 155° (decomp.) (Found: OMe, Nil). The compound is thus 2-methyl arabinose.

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[*Received, October 20th*, 1947.]

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71. *Pyrazine Derivatives. Part VIII. Synthesis of Acylamidopyrazines from Aminomethyl Ketones.*

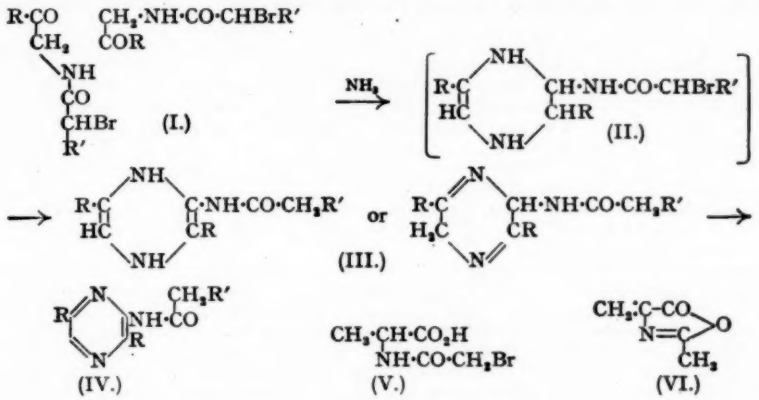
By G. T. NEWBOLD, F. S. SPRING, and WILFRED SWEENY.

The reaction described in Part V of this series whereby an α-bromopropionyl derivative of an aminomethyl ketone is converted into an acylamidopyrazine has been successfully extended to some corresponding phenylbromoacetyl derivatives. The mechanism of the reaction is discussed.

IN Part V (*J.*, 1948, 1855) we have shown that treatment of an α-bromopropionyl derivative of an aminomethyl ketone (I; R′ = Me) with ammonia gives an α-propionamidopyrazine derivative (IV; R′ = Me) in high yield. Evidence concerning the mechanism of the reaction has been obtained by an examination of further cases. Our experience has hitherto been limited to α-bromopropionyl derivatives of different aminomethyl ketones (aminoacetone, 1-aminobutan-2-one, ω-aminoacetophenone), and it was considered desirable to extend this experience to other bromoacyl derivatives of aminomethyl ketones. Condensation of ω-aminoacetophenone with phenylbromoacetyl bromide gave ω-(*phenylbromoacetamido*)*acetophenone* (I; R = R′ = Ph); this on treatment with ammonia gave 3-*phenylacetamido*-2 : 5-*diphenylpyrazine* (IV; R = R′ = Ph), the structure of which was established by alkaline hydrolysis to 3-amino-2 : 5-diphenylpyrazine and phenylacetic acid.

Condensation of aminoacetone with phenylbromoacetyl bromide gave *phenylbromoacetamidoacetone* (I; R = Me, R′ = Ph), treatment of which with ammonia gave a compound, $C_{14}H_{17}ON_3$. This compound is 3-*phenylacetamido*-2 : 5-*dimethyldihydropyrazine*, since on standing in air or on oxidation under mild conditions with hydrogen peroxide it is converted into 3-*phenylacetamido*-2 : 5-*dimethylpyrazine* (IV; R = Me, R′ = Ph), the structure of which was established by alkaline hydrolysis to 3-amino-2 : 5-dimethylpyrazine and phenylacetic acid, and by its synthesis from 3-amino-2 : 5-dimethylpyrazine. If the reaction between ammonia and phenylbromoacetamidoacetone is carried out in an iron autoclave, 3-phenylacetamido-2 : 5-dimethylpyrazine is obtained and not the dihydro-derivative.

The isolation of a dihydropyrazine derivative is of some importance in a consideration of the mechanism of the general reaction. Condensation of two moles of a bromoacylamidomethyl ketone (I) with one mole of ammonia may give rise to a tetrahydropyrazine derivative such as



(II). The conversion of this tetrahydropyrazine into the aromatic pyrazine (IV) is most probably a two-stage process in which the dihydropyrazine (III) is an intermediate. Although a dihydropyrazine intermediate has been isolated in only one case of the general reaction, this is not surprising since dihydropyrazine derivatives, which are intermediates in numerous pyrazine syntheses, are readily oxidised to the corresponding aromatic pyrazine, and their isolation is either difficult or impossible. We believe that the tetrahydropyrazine (II) is oxidised to a dihydropyrazine by a simultaneous reductive dehalogenation of the bromoacyl group. In support of this view, we find that the general reaction is dependent upon the presence of a halogen atom in the acyl group, propionamidoacetone being recovered unchanged after treatment with ammonia.

The general reaction can now be formulated as shown at (I)—(IV). The step (II) ⟶ (III) bears a formal resemblance to the formation of azlactones such as (VI) from α′-halogenoacyl derivatives of α-amino-acids such as (V) (Bergmann and Stern, *Annalen*, 1926, **448**, 20; Bergmann, Kann, and Mieckley, *ibid.*, **449**, 135). The position of the double bonds in the dihydropyrazine (III) is an arbitrary choice; in the preparation of 3-phenylacetamido-2 : 5-dimethylpyrazine (IV; R = Me, R′ = Ph) the isolated intermediate dihydropyrazine does not exhibit selective absorption in the ultra-violet region of the spectrum and consequently it does not contain a conjugated system of double bonds.

Experimental.

ω-(Phenylbromoacetamido)acetophenone.—A suspension of dry powdered ω-aminoacetophenone hydrochloride (10 g.) in dry chloroform (30 c.c.) was mixed with a solution of phenylbromoacetyl bromide (18 g.) in dry chloroform (30 c.c.). The mixture was rapidly stirred and treated at 0° with a solution of *N*-methylmorpholine (13·5 g.) in dry chloroform (30 c.c.) added dropwise during 1 hour. The mixture was stirred at room temperature for a further hour, and the chloroform solution washed successively with water, dilute hydrochloric acid, dilute sodium carbonate solution, and water. The dried (Na_2SO_4) solution was evaporated under reduced pressure. The crystalline solid was recrystallised from chloroform from which *ω-(phenylbromoacetamido)acetophenone* separated as prisms (yield 90%); for analysis it was recrystallised from light petroleum (b. p. 100—120°) from which it separated as needles, m. p. 119° (Found : C, 57·8; H, 4·3; N, 4·4. $C_{16}H_{14}O_2NBr$ requires C, 57·8; H, 4·2; N, 4·2%).

Phenylbromoacetamidoacetone was obtained in 85% yield from aminoacetone hydrochloride and phenylbromoacetyl bromide by the above procedure. It separated from benzene–light petroleum (b. p. 40—60°) as needles and from light petroleum (b. p. 100—120°) as plates, m. p. 108° (Found : C, 49·0; H, 4·3; N, 5·3. $C_{11}H_{12}O_2NBr$ requires C, 48·9; H, 4·4; N, 5·2%).

3-Phenylacetamido-2 : 5-diphenylpyrazine.—A solution of ω-(phenylbromoacetamido)acetophenone (6 g.) and ammonium iodide (1 g.) in liquid ammonia (200 c.c.) was kept in an autoclave at room temperature for 16 hours. Evaporation of the ammonia gave an oily residue which was extracted with boiling acetone (5 × 20 c.c.). The extract was concentrated, and on cooling deposited *3-phenylacetamido-2 : 5-diphenylpyrazine* as long needles, which, after recrystallisation from the same solvent, had m. p. 194° (yield, 25%) (Found : C, 79·2; H, 5·2; N, 11·4. $C_{24}H_{19}ON_3$ requires C, 78·9; H, 5·2; N, 11·5%).

3-Amino-2 : 5-diphenylpyrazine.—A suspension of 3-phenylacetamido-2 : 5-diphenylpyrazine (0·5 g.) in 0·1N-sodium hydroxide was refluxed for 3 days. The mixture was cooled, and the yellow solid collected by filtration and washed with water. Recrystallisation from ethanol gave 3-amino-2 : 5-diphenylpyrazine as yellow plates, m. p. 186° either alone or when mixed with an authentic specimen (yield,

quantitative). The alkaline filtrate from the reaction mixture was exactly neutralised with 0·1N-hydrochloric acid and evaporated to dryness under reduced pressure. The residue was extracted with ether, and the extract evaporated to give phenylacetic acid (0·11 g.), m. p. and mixed m. p. 74°. The acid was characterised by conversion into its amide by successive treatment with thionyl chloride and ammonia. Phenylacetamide was obtained from water as plates, m. p. 157° either alone or when mixed with an authentic specimen.

3-*Phenylacetamido*-2 : 5-*dimethyldihydropyrazine*.—Treatment of phenylbromoacetamidoacetone with liquid ammonia and ammonium iodide (using an autoclave fitted with a glass liner) as described above gave a product which was extracted with boiling benzene. Evaporation of the extract gave a crystalline solid which was recrystallised from benzene to give 3-*phenylacetamido*-2 : 5-*dimethyldihydropyrazine* as plates, m. p. 154° (yield, 60%). For analysis it was recrystallised from light petroleum (b. p. 100—120°) (Found : C, 69·9; H, 7·3; N, 17·1. $C_{14}H_{17}ON_3$ requires C, 69·1; H, 7·0; N, 17·3%). When the reaction was carried out in an iron autoclave without a glass liner, the product was 3-phenylacetamido-2 : 5-dimethylpyrazine, m. p. and mixed m. p. 130°.

The dihydropyrazine is unstable in air, the m. p. gradually falling. After 3 weeks the m. p. was less than 130°, after 3 months it was 116—124°, and a mixture with 3-phenylacetamido-2 : 5-dimethylpyrazine had an intermediate m. p.

3-*Phenylacetamido*-2 : 5-*dimethylpyrazine*.—A solution of 3-phenylacetamido-2 : 5-dimethyldihydropyrazine (0·14 g.) in methanol (2 c.c.) was treated with hydrogen peroxide solution (100 vol., 1 c.c.) and shaken overnight at room temperature. The solution was evaporated under reduced pressure to give 3-*phenylacetamido*-2 : 5-*dimethylpyrazine* (0·12 g.); this separated from light petroleum (b. p. 100—120°) as plates, m. p. 130° (Found : C, 69·7; H, 6·2; N, 17·3. $C_{14}H_{15}ON_3$ requires C, 69·7; H, 6·2; N, 17·4%).

3-*Amino*-2 : 5-*dimethylpyrazine*.—A solution of 3-phenylacetamido-2 : 5-dimethylpyrazine (0·5 g.) in 0·1N-sodium hydroxide (30 c.c.) was refluxed for 13 hours. The solution was cooled and extracted with ether. The ethereal solution was evaporated, and the residue crystallised from benzene to yield 3-amino-2 : 5-dimethylpyrazine (0·25 g.) as needles, m. p. 112°, undepressed when mixed with an authentic specimen. The picrate had m. p. 206° either alone or when mixed with 3-amino-2 : 5-dimethylpyrazine picrate. The aqueous alkaline phase from the ether extraction was acidified with dilute hydrochloric acid and evaporated to dryness under reduced pressure. Extraction of the residue with ether gave phenylacetic acid (0·2 g.), m. p. 69°, characterised by conversion into the amide which separated from water as plates, m. p. and mixed m. p. 157°.

3-Amino-2 : 5-dimethylpyrazine (50 mg.) was refluxed with phenylacetyl chloride (0·2 c.c.) in dry benzene (5 c.c.) for 3 hours. The mixture was cooled, and the solid collected and shaken with a mixture of 3N-sodium hydroxide (10 c.c.) and ether (100 c.c.). The ethereal layer was dried (Na_2SO_4) and evaporated. Recrystallisation of the residue from light petroleum (b. p. 100—120°) gave 3-phenylacetamido-2 : 5-dimethylpyrazine as plates, m. p. 130° either alone or when mixed with the specimen described above.

Grateful acknowledgment is made of grants from the Department of Scientific and Industrial Research.

THE ROYAL TECHNICAL COLLEGE, GLASGOW. [*Received, March 5th*, 1948.]

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72. *Furano-compounds. Part IX. The Synthesis of Kellin and Related Compounds.*

By J. R. CLARKE and ALEXANDER ROBERTSON.

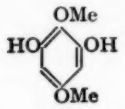
The synthesis of kellinone (V; R and R_1 = H), a degradation product of the furanochromone, kellin, has been achieved by way of the stages (I), (II; R = H), (II; R = Ph·CH_2), (III), (IV; R = Ph·CH_2), (IV; R = H), and (V; R = CO_2H, R_1 = H). Obtained from (V; R and R_1 = H) by the standard method, the diketone (V; R = H, R_1 = Ac) is readily converted into kellin (VI), identical with natural material.

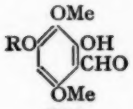
By means of the accessible intermediate kellinone a series of furano-flavanones and -flavones has been synthesised.

IN their analytical studies on the structure of kellin, a major constituent of the alcoholic extract of *Ammi visnaga* seeds, Späth and Gruber (*Ber.*, 1938, **71**, 106) obtained a ketone, kellinone, for which, since it could be degraded to furan-2 : 3-dicarboxylic acid and to 2 : 5-dimethoxy-4 : 6-diethoxy-3-acetylbenzoic acid, they proposed the structure (V; R and R_1 = H). In consequence these authors concluded that kellin was the linear furanochromone (VI) and is thus the analogue of the furanocoumarin, *iso*pimpinellin. This assignation of structure (VI) to kellin has now been completely vindicated by the following synthesis according to the general procedure outlined in Part VIII (*J.*, 1948, 2260).

From the dimethoxyresorcinol (I) an excellent yield of the 2 : 4-*dihydroxy*-3 : 6-*dimethoxybenzaldehyde* (II; R = H) was obtained by Gattermann's procedure, and on benzylation this substance gave the *benzyl ether* (II; R = Ph·CH_2), the orientation of which follows from its ferric reaction in alcohol and its ultimate conversion into (IV; R = Ph·CH_2). Interaction of (II; R = Ph·CH_2) with ethyl bromoacetate in the presence of potassium carbonate in boiling

acetone gave rise to the *phenoxyacetate* (III); this, on cyclisation with alcoholic sodium ethoxide, furnished the *coumarone-2-carboxylate* (IV; R = Ph·CH_2) which was debenzylated by means of hydrogen and a palladium–charcoal catalyst, yielding *ethyl 6-hydroxy-4 : 7-dimethoxycoumarone-2-carboxylate* (IV; R = H). The presence of the carbethoxy-group in the 2-position of (IV; R = Ph·CH_2) serves to inhibit the saturation of the reactive double bond in the furan residue during hydrogenolysis, whilst in (IV; R = H) this group serves to protect the reactive 2-position of the furan residue during the subsequent Friedel–Crafts reaction.


(I.)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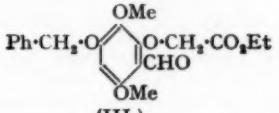
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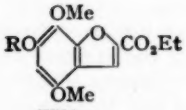
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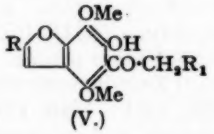
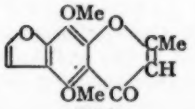
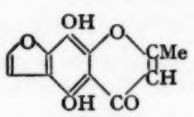

(V.)


(VI.)

The condensation of (IV; R = H) with acetyl chloride by means of aluminium chloride in nitrobenzene and subsequent isolation of the product with the aid of aqueous sodium hydroxide furnished the *ketonic acid* (V; R = CO_2H, R_1 = H), and not the expected ester (V; R = CO_2Et, R_1 = H). On decarboxylation, the acid (V; R = CO_2H, R_1 = H) gave rise to kellinone (V; R = H, R_1 = H), identical with a specimen prepared from natural kellin. A small amount of the *acetate* of (IV; R = H) invariably accompanied the compound (V; R = CO_2H, R_1 = H) in the Friedel–Crafts reaction product. The interaction of kellinone with ethyl acetate and sodium resulted in the formation of the *diketone* (V; R = H, R_1 = Ac) which on cyclisation yielded kellin (VI), identical with natural material (cf. Späth and Gruber, *loc. cit.*). In agreement with this structure (VI), the methyl group in the 2-position of the chromone residue readily reacted with piperonal in alkaline media to form a *styrylchromone*.

In the course of attempts to prepare the parent dihydroxyfuranochromone (VII) from kellin, it was found that on being subjected to demethylation by means of boiling hydriodic acid kellin gave rise to a somewhat resinous product from which only one crystalline *substance* has been isolated so far; variation of the conditions employed in the demethylation process gave the same result. Methylation of this substance by the methyl iodide–potassium carbonate method yielded a dimethyl ether, isomeric and not identical with kellin, for which we propose the name iso*kellin*. The retention of the 2-methylchromone nucleus in *iso*kellin is demonstrated by its ability to form a *styryl* derivative with piperonal under the usual conditions.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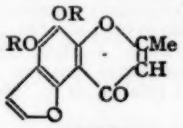
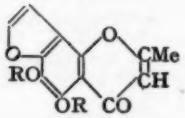
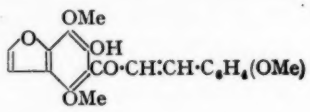

(VIII.)

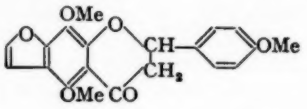

(IX.)

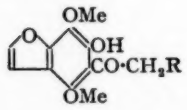
Taking into account the behaviour of visnagin (Part VIII, *loc. cit.*) under similar conditions, it would seem that the demethylation and the ultimate formation of an isomeride of kellin in this manner may involve either (*a*) the furan ring with the compound (VIII; R = H) as an intermediate, or (*b*) the pyrone ring with (IX; R = H) as an intermediate. Consequently *iso*kellin may be represented by either formula (VIII; R = Me) or (IX; R = Me), of which, by analogy with *iso*visnagin (Part VIII, *loc. cit.*), the former is regarded as being the more probable, but a final decision on this point must await an independent synthesis of *iso*kellin.

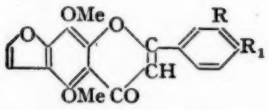
So far as we are aware the only example of a known naturally occurring furanoflavone is karanjin, but it seems likely that further examples of this group will be brought to light (*e.g.*, see Baker and Simmonds on ginkgetin, *J.*, 1940, 1370), and in view of the accessibility of kellinone we have synthesised typical furano-flavanones and -flavones having this nucleus. The condensation of (V; R = H, R_1 = H) with anisaldehyde by the standard method gave rise to the *styryl ketone* (X), and on being boiled with alcoholic phosphoric acid this was converted into an equilibrium mixture of (X) and the *flavanone* (XI) from which (XI) was isolated

by fractional crystallisation. In this cyclisation the almost complete absence of re-inification (polymerisation) of the furano-derivatives in hot acidic reagents is remarkable.

(X.) 

 (XI.)

(XII.) 

 (XIII.)

Similarly the *styryl ketone* from (V; R = H, R_1 = H) and piperonal gave rise to a mixture from which 5 : 8-*dimethoxy*-3'' : 4''-*methylenedioxyfurano*(4' : 5' : 6 : 7)*flavanone* was isolated.

For the synthesis of the flavones of type (XIII) from kellinone we preferred the diketone method to the well-known Robinson aroylation process, thus avoiding the application of high temperatures as well as the formation of 3-acylflavone derivatives. By means of the migration process discovered by Baker (*J.*, 1933, 1381; 1940, 1370; cf. Mahal and Venkataraman, *J.*, 1934, 1767) the *benzoate*, p-*methoxybenzoate*, and *veratroate* of kellinone were converted into the corresponding diketones (XII; R = benzoyl), (XII; R = *p*-methoxybenzoyl), and (XII; R = veratroyl) and on cyclisation the latter furnished respectively the furanoflavones (XIII; R = H, R_1 = H), (XIII; R = H, R_1 = OMe), and (XIII; R and R_1 = OMe).

Experimental.

2 : 5-*Dimethoxyresorcinol*.—This phenol was prepared essentially according to the route devised by Robinson and his co-workers (*J.*, 1929, 74) with the following modifications. In the benzylation of pyrogallol a 60% increase in the amount of potassium carbonate employed doubled the yield of tribenzyl ether, and in the oxidation of the ether (40 g.) with nitric acid (*d* 1·185) instead of acid (*d* 1·19) the yield of quinone was increased from 15 g. to 18 g. 2 : 6-Dibenzyloxyquinol (20 g.) was methylated with methyl sulphate (27 g., added in 4 portions) and potassium carbonate (100 g.) in boiling acetone (250 ml.) in the course of 4 hours. The mixture was treated with water (800 ml.), and 24 hours later the dimethyl ether (21 g.) was collected and crystallised from alcohol, forming colourless prisms (18·5 g.). This ether (6 g.), dissolved in methanol (400 ml.), was debenzylated by means of hydrogen and a 10% palladium–charcoal catalyst (2 g.) in the course of 35 minutes, and after the separation of the catalyst the solution was evaporated in a vacuum and the residual solid crystallised from hot water (90 ml.), giving the dihydrate of 2 : 5-dimethoxyresorcinol in plates (2·85 g.), m. p. 61—62°, which on being dried over phosphoric oxide in a vacuum yielded anhydrous material, m. p. 87°.

2 : 4-*Dihydroxy*-3 : 6-*dimethoxybenzaldehyde* (II; R = H).—A solution of the foregoing dimethoxyresorcinol (10 g.) in ether (200 ml.) containing hydrogen cyanide (10 ml.) was saturated with hydrogen chloride at 0°, and next day the crystalline aldimine was collected, washed with ether, and dissolved in water (300 ml.). When this solution was almost neutralised with solid sodium carbonate and then heated on the water-bath for ½ hour, the *aldehyde* quickly separated. Next day the solid (10·5 g.) was collected, washed, and crystallised from methanol (charcoal), forming elongated, faintly yellow needles, m. p. 197°, almost insoluble in water, sparingly soluble in cold alcohol, benzene, or chloroform, and readily soluble in acetone [Found: C, 54·1; H, 5·0; OMe, 29·8. $C_7H_4O_3(OMe)_2$ requires C, 54·5; H, 5·1; OMe, 31·3%]. In alcohol the compound gives a dark red ferric reaction. The 2 : 4-*dinitrophenylhydrazone* separated from dilute acetic acid in tiny dark red prisms, m. p. 290° (Found: N, 14·4. $C_{15}H_{14}O_8N_4$ requires N, 14·8%).

Ethyl 3-*Benzyloxy*-2 : 5-*dimethoxy*-6-*formylphenoxyacetate* (III).—The foregoing aldehyde (4 g.) was monobenzylated with benzyl bromide (2·8 ml.) and potassium carbonate (12 g.) in boiling acetone (200 ml.) in the course of 1¾ hours, and, after the removal of the potassium salts (wash with hot acetone), the solution was evaporated and the product triturated with water. Crystallised from methanol and then ethanol, the *monobenzyl ether* (II; R = Ph·CH_2) (3·8 g.) formed colourless needles, m. p. 125°, having a dark red alcoholic ferric reaction (Found: C, 66·7; H, 5·5. $C_{16}H_{16}O_5$ requires C, 66·6; H, 5·6%). This compound is readily soluble in benzene, acetone, or chloroform. The 2 : 4-*dinitrophenylhydrazone* separated from dilute acetic acid in scarlet plates, m. p. 272° (Found: N, 12·0. $C_{22}H_{20}O_8N_4$ requires N, 11·9%).

A solution of the benzyl ether (4 g.) in acetone (75 ml.), containing ethyl bromoacetate (2 ml.) and potassium carbonate (10 g.), was refluxed for 5 hours, *i.e.*, until a test portion of the product gave a negative ferric reaction, and the *phenoxyacetate* (III) isolated as an oil which gradually crystallised. This material was washed with a little ether (20 ml.) to remove traces of oily impurities and then purified from a large volume of light petroleum (b. p. 60—80°), forming long, slender prisms (5·0 g.), m. p. 85°, having a negative ferric reaction (Found: C, 64·5; H, 6·0. $C_{20}H_{22}O_7$ requires C, 64·2; H, 5·9%). The *semicarbazone* crystallised from acetic acid in needles, m. p. 154° (Found: N, 9·6. $C_{21}H_{25}O_7N_3$ requires N, 9·7%).

Ethyl 6-*Hydroxy*-4 : 7-*dimethoxycoumarone*-2-*carboxylate* (IV; R = H).—Alcoholic sodium ethoxide (from 0·5 g. of sodium and 20 ml. of alcohol) was added to a suspension of ethyl 3-benzyloxy-2 : 5-dimethoxy-6-formylphenoxyacetate (6 g.) in absolute alcohol (40 ml.), and the mixture agitated until

the solid had dissolved (10 minutes). On being kept at room temperature (40 minutes), the mixture gradually deposited *ethyl 6-benzyloxy-4 : 7-dimethoxycoumarone-2-carboxylate* (IV; R = Ph·CH_2) as a mass of yellow prisms which were collected and washed with a little cold alcohol and then with water; a further small quantity of the product was obtained by addition of water to the filtrate. Recrystallised from 95% alcohol, the coumarone formed almost colourless prisms (2·8 g.), m. p. 87°, slightly soluble in methanol or warm light petroleum and readily soluble in acetone or ethyl acetate (Found: C, 67·6; H, 5·6. $C_{20}H_{20}O_6$ requires C, 67·5; H, 5·6%). On being warmed, the yellow solution of the coumarone in sulphuric acid becomes red.

Acidification of the aqueous filtrate from the crude ester gave *3-benzyloxy-2 : 5-dimethoxy-6-formylphenoxyacetic acid* which on repeated crystallisation from water, formed white needles, m. p. 142°, sparingly soluble in alcohol or benzene (Found: C, 62·8; H, 5·3. $C_{18}H_{18}O_7$ requires C, 62·4; H, 5·2%).

The absorption of hydrogen (150 ml.; theory 130 ml.) by a solution of the foregoing benzyl ether of the coumarone (2 g.) in acetic acid (100 ml.) containing a palladium–charcoal catalyst, was complete in 10—15 minutes, and after removal of the catalyst by filtration the filtrate was diluted with water (300 ml.). Next day the resulting *ethyl 6-hydroxy-4 : 7-dimethoxycoumarone-2-carboxylate* (IV; R = H) which had separated was collected and recrystallised from aqueous alcohol, forming colourless slender needles (1·3 g.), m. p. 131°, readily soluble in acetone or ethyl acetate and having a red sulphuric acid reaction (Found: C, 59·0; H, 5·3. $C_{13}H_{14}O_6$ requires C, 58·7; H, 5·3%). Prepared by the acetyl chloride–pyridine method, the *acetate* of this compound crystallised from methanol in short prisms, m. p. 104° (Found: C, 58·2; H, 5·4. $C_{15}H_{16}O_7$ requires C, 58·4; H, 5·2%).

6-Hydroxy-4 : 7-dimethoxy-5-acetylcoumarone (*Kellinone*) (V; R and R_1 = H).—Aluminium chloride (4 g.) was added in several portions in the course of 15 minutes to a solution of ethyl 6-hydroxy-4 : 7-dimethoxycoumarone-2-carboxylate (2 g.) and acetyl chloride (2 ml.) in pure nitrobenzene (70 ml.) kept below 4°. The mixture, which was vigorously stirred, was kept at about 4° for 2 hours and then at room temperature for 48 hours, then poured on ice (500 g.). 3 Hours after the addition of light petroleum (b. p. 60—80°) (150 ml.), the aqueous layer was removed and the light petroleum–nitrobenzene layer was extracted with aqueous sodium hydrogen carbonate (50 ml. × 2) and then with 6% aqueous sodium hydroxide (50 ml. × 5). Acidification of the combined aqueous sodium hydroxide extracts with hydrochloric acid gave a flocculent precipitate of *6-hydroxy-4 : 7-dimethoxy-5-acetylcoumarone-2-carboxylic acid* (V; R = CO_2H, R_1 = H) which crystallised from methanol in tiny yellow needles (0·35 g.), m. p. 252°, moderately soluble in benzene or chloroform, and having a green ferric reaction in alcohol [Found: C, 55·6; H, 4·1; OMe, 19·9. $C_{11}H_6O_5(OMe)_3$ requires C, 55·7; H, 4·3; OMe, 22·1%].

Acidification of the combined sodium hydrogen carbonate washings gave a small quantity of material having a reddish ferric reaction, whilst distillation of the light petroleum and nitrobenzene in a current of steam after the separation of the foregoing acid (V; R = CO_2H, R_1 = H) left a product which was found by comparison with an authentic specimen to be the acetate of the initial coumarone (IV; R = Ac), and which, on deacetylation by treatment with concentrated sulphuric acid for 2 minutes followed by addition of excess of water, gave a precipitate of the parent coumarone (IV; R = H), m. p. 130—131°, after purification.

The coumaronecarboxylic acid (0·3 g.) was decarboxylated by being gently refluxed with absolute quinoline (10 ml.) containing copper bronze (0·3 g.) for 25 minutes. After addition of ether (50 ml.), the filtered solution was extracted with 2N-hydrochloric acid (20 ml. × 5) to remove quinoline, then with aqueous sodium hydrogen carbonate to remove traces of unchanged acid, and finally with 7% aqueous sodium hydroxide (15 ml. × 6). The combined alkaline extracts were acidified with hydrochloric acid, saturated with ammonium sulphate, and extracted several times with ether. Evaporation of the dried ethereal extracts left a brown oil which gradually solidified, and then on crystallisation from aqueous methanol gave 6-hydroxy-4 : 7-dimethoxy-5-acetylcoumarone in light brown prisms (0·075 g.) which on repeated purification from the same solvent (charcoal) formed small yellow prisms (0·05 g.), m. p. 100°, having a green ferric reaction and being identical with a natural specimen of kellinone [Found: C, 60·7; H, 5·2; OMe, 25·7. Calc. for $C_{10}H_6O_3(OMe)_2$: C, 61·0; H, 5·1; OMe, 26·3%]. The *2 : 4-dinitrophenylhydrazone* formed slender brick-red needles, m. p. 245°, from dilute acetic acid (Found: N, 13·5. $C_{18}H_{16}O_9N_4$ requires N, 13·5%).

Attempts to decarboxylate the acid by sublimation in a vacuum in the presence of copper bronze gave very poor yields of impure kellinone.

Kellin (VI).—When the vigorous reaction between kellinone (2 g.), ethyl acetate (25 ml.), and sodium (2 g., added in small pieces) had subsided the mixture was heated on the steam-bath for 5 hours with addition of more sodium (1 g., in small pieces) after 2 hours. After addition of a little methanol to destroy traces of metallic sodium, and subsequent dilution with water (300 ml.), the mixture was acidified with acetic acid, giving a brown oil which gradually solidified, and was then dissolved in much light petroleum (b. p. 80—100°). Part of the solvent was distilled, leaving a saturated solution which on cooling deposited crystalline material; recrystallisation of this several times from benzene–light petroleum (b. p. 60—80°) gave the *diketone* (V; R = H, R_1 = Ac) in small yellow prisms (0·9 g.), m. p. 105°, having a red ferric reaction in alcohol (Found: C, 60·5; H, 5·1. $C_{14}H_{14}O_6$ requires C, 60·4; H, 5·0%).

When a solution of the diketone (0·5 g.) in alcohol (8 ml.) containing 4 drops of concentrated hydrochloric acid was boiled for 1 minute, the resulting yellowish solution, on cooling, deposited kellin in colourless elongated prisms (0·3 g.) which after recrystallisation from aqueous alcohol had m. p. 153°, undepressed on admixture with a natural specimen [Found: C, 64·2; H, 4·6; OMe, 22·4. Calc. for $C_{12}H_6O_3(OMe)_3$: C, 64·6; H, 4·6; OMe, 23·8%].

On being heated on the steam-bath for 10 minutes, the yellow mixture of kellin (1 g.), piperonal (1 g.), sodium methoxide (from 0·3 g. of sodium), and methanol (35 ml.) became deep orange, and on cooling deposited the *styryl* derivative which formed yellow needles (1·2 g.), m. p. 239°, from dilute acetic acid (Found: C, 67·5; H, 4·2. $C_{22}H_{16}O_7$ requires C, 67·3; H, 4·1%). This compound, which is sparingly soluble in alcohol, benzene, or ethyl acetate, gives a dark red sulphuric acid reaction.

Demethylation of Kellin.—Hydriodic acid (28 ml.; *d* 1·7, freshly distilled over red phosphorus) was

carefully added to a cooled mixture of kellin (2 g.) and acetic anhydride (20 ml.), the resulting clear red solution was gently refluxed (oil-bath) for ½ hour, and the cooled mixture was poured on ice (70 g.), giving rise to a yellow flocculent precipitate mixed with a small amount of a brown oil. Sufficient saturated aqueous sodium hydrogen sulphite to remove liberated iodine was added, and the *compound* was collected 24 hours later and repeatedly crystallised from aqueous acetic acid and then from a little absolute acetic acid, forming deep yellow prisms (0·5 g.), m. p. 252°, sparingly soluble in the usual organic solvents except acetic acid, and giving a green ferric reaction in alcohol (Found: C, 61·7; H, 3·5. $C_{12}H_8O_5$ requires C, 62·0; H, 3·5%). When gently warmed, the yellow solution of this compound in sulphuric acid became green, blue, and then dark crimson. On being shaken or kept in air, the green solution of the compound in 8% aqueous sodium hydroxide rapidly became dark brown. The mother liquors left on purification of the demethylation product gave only intractable tarry material.

When a mixture of the foregoing product (0·5 g.), acetone (50 ml.), potassium carbonate (3 g.), and methyl iodide (1 ml.) was refluxed for 28 hours, the chromone gradually dissolved and the solution became almost colourless. After separation of the potassium salts (wash 3 times with hot acetone), the solution was evaporated and the residue triturated with water. Crystallisation of the resulting solid from dilute methanol gave iso*kellin* in cream-coloured needles (0·44 g.), m. p. 176°, insoluble in aqueous alkali or cold light petroleum, moderately soluble in alcohol, and readily soluble in the other common organic solvents [Found: C, 64·7; H, 4·4; OMe, 20·5. $C_{12}H_6O_3(OMe)_2$ requires C, 64·6; H, 4·6; OMe, 23·8%]. On being warmed, the yellow solution of the substance in concentrated sulphuric acid becomes green, then blue, and finally scarlet red.

A mixture of *iso*kellin (0·6 g.), piperonal (0·6 g.), sodium methoxide (from 0·2 g. of sodium), and methanol (30 ml.) was refluxed for 15 minutes and then kept at room temperature for 48 hours. Crystallisation of the resulting yellow product from dilute acetic acid gave the *styryl* derivative in slender yellow needles (0·6 g.), m. p. 226°, having a dark red sulphuric acid reaction (Found: C, 67·6; H, 4·4. $C_{22}H_{16}O_7$ requires C, 67·3; H, 4·1%).

5 : 8 : 4''-*Trimethoxyfurano*(4' : 5' : 6 : 7)*flavanone* (XI).—50% Aqueous sodium hydroxide (4 g.) was added to a warm solution of kellinone (2 g.) and anisaldehyde (1·3 g.) in alcohol (25 ml.), the red mixture refluxed for 1 hour on the steam-bath, and the cooled dark red solution diluted with water (100 ml.) and acidified (litmus) with 2N-hydrochloric acid. Thus precipitated, the resulting red-brown oil slowly solidified, and on crystallisation from methanol gave 6-*hydroxy*-4 : 7 : 4'-*trimethoxy*-5-*cinnamoylcoumarone* (X) (2·2 g.) in yellow needles, m. p. 141°, having a dark red ferric reaction and a similar sulphuric acid reaction (Found: C, 67·6; H, 5·1. $C_{20}H_{18}O_6$ requires C, 67·7; H, 5·1%).

When a mixture of phosphoric acid (from 5·5 g. of oxide and 10 ml. of water), alcohol (125 ml.), and the aforementioned styryl ketone (1 g.) was refluxed for 48 hours and part of the solvent (50 ml.) evaporated under reduced pressure, the residual liquor gradually deposited crystalline material. By successive evaporation of the filtrate from this solid (A) two further crops (B) and (C) were obtained, and the residual liquor was then poured into water, giving a yellow precipitate (D). Products (B) and (C), which gave only a faint ferric reaction, were combined and crystallised 3 times from methanol, giving the *flavanone* (XI) in tiny, glistening, orange plates (0·23 g.), m. p. 141°, having a negative ferric reaction and a red sulphuric acid reaction (Found: C, 67·8; H, 5·2%). A mixture of the flavanone and unchanged styryl ketone had m. p. 115—120°.

The fractions (A) and (D) consisted almost wholly of unchanged styryl ketone, m. p. and mixed m. p. 141°, after purification.

5 : 8-*Dimethoxy*-3'' : 4''-*methylenedioxyfurano*(4' : 5' : 6 : 7)*flavanone*.—Kellinone (2 g.) was condensed with piperonal (1·3 g.) by the procedure employed for anisaldehyde; on crystallisation from aqueous acetone, the resulting 6-*hydroxy*-4 : 7-*dimethoxy*-3' : 4'-*methylenedioxy*-5-*cinnamoylcoumarone* formed tiny red plates with a bronze sheen (2 g.), m. p. 153°, having a dark red ferric reaction in alcohol and a red sulphuric acid reaction (Found: C, 65·4; H, 4·4. $C_{20}H_{14}O_7$ requires C, 65·2; H, 4·3%).

The styryl ketone (1 g.) was cyclised with phosphoric acid in boiling alcohol, and the solution concentrated as in the case of the foregoing analogue. From the concentrated reaction mixture fractions (A) and (B) were obtained, of which (A) consisted of a mixture of yellow and red crystals. Extraction of (A) with boiling methanol removed the red crystals which consisted of unchanged ketone; recrystallisation of the yellow residue from aqueous acetone gave the flavanone in pale yellow rectangular prisms (0·2 g.), m. p. 181°, having a negative ferric reaction and a red sulphuric acid reaction (Found: C, 65·4; H, 4·3%). Fraction (B) consisted of unchanged styryl ketone, m. p. 153°, after purification.

5 : 8-*Dimethoxyfurano*(4' : 5' : 6 : 7)*flavone* (XIII; R and R_1 = H).—Benzoyl chloride (3 ml.) was added in portions during the course of 5 minutes to an agitated solution of kellinone (4 g.) in pyridine (25 ml.), and the mixture gently warmed for 10 minutes. Next day the orange-red mixture was poured into water (200 ml.), and after having been well washed with dilute hydrochloric acid and then with water the resulting *benzoate* was crystallised from methanol, forming colourless rhombic plates (4·3 g.), m. p. 97°, insoluble in aqueous sodium hydroxide and having a negative ferric reaction (Found: C, 67·3; H, 5·0. $C_{19}H_{16}O_6$ requires C, 67·1; H, 4·7%).

A mixture of this ester (3 g.) and powdered sodamide (6 g.) was heated in toluene (60 ml.) on the steam-bath with occasional shaking for 10 hours, and the brown solid collected, washed with benzene, dried, and dissolved in iced water. On being saturated with carbon dioxide, the solution deposited a red-brown oil which gradually solidified, and on crystallisation from methanol gave the *diketone* (XII; R = Ph·CO) in bright red needles (1·3 g.). Recrystallisation of this material gave a mixture of red and yellow needles, m. p. 103°, from which, by crystallisation from benzene–light petroleum (b. p. 60—80°), red needles, m. p. 103°, were isolated (Found: C, 67·4; H, 4·7. $C_{19}H_{16}O_6$ requires C, 67·1; H, 4·7%). This compound gives a dark red ferric reaction.

When the orange-red solution of the foregoing diketone (0·5 g.) in acetic acid (25 ml.) containing 5 drops of concentrated hydrochloric acid was boiled for 1 minute, the colour first changed to a deeper red and then became yellow; on addition of water (150 ml.) the solution deposited the *flavone* which formed short yellow prisms (0·3 g.), m. p. 180°, after slight sintering at 177°, having a negative ferric

reaction and a red sulphuric acid reaction (Found: C, 70·8; H, 4·5. $C_{19}H_{14}O_5$ requires C, 70·8; H, 4·4%).

5 : 8 : 4″-*Trimethoxyfurano*(4′ : 5′ : 6 : 7)*flavone* (XIII; R = H, R_1 = OMe).—Prepared by the method used for the benzoate, the p-*methoxybenzoate* of kellinone formed colourless plates, m. p. 117°, from methanol, readily soluble in the usual organic solvents except alcohol and light petroleum (Found: C, 64·7; H, 5·3. $C_{20}H_{18}O_7$ requires C, 64·9; H, 4·9%). By means of sodamide (5 g.) in toluene (50 ml.) on the steam-bath for 10 hours this ester (2·5 g.) was converted into the isomeric *diketone* (XII; R = *p*-methoxybenzoyl) which formed yellow prisms (1·4 g.), m. p. 169°, from benzene–light petroleum (b. p. 60—80°), sparingly soluble in alcohol and moderately soluble in benzene, acetone, or acetic acid (Found: C, 65·3; H, 5·0. $C_{20}H_{18}O_7$ requires C, 64·9; H, 4·9%). In alcohol the ferric reaction of this substance is greenish yellow, rapidly changing to dark red.

Cyclisation of this diketone (0·5 g.) with boiling acetic acid (25 ml.) containing a little hydrochloric acid gave rise to the *flavone* (XIII; R = H, R_1 = OMe) which separated from methanol and then ethanol in pale yellow needles (0·35 g.), m. p. 184°, moderately soluble in benzene or acetone and readily soluble in chloroform (Found: C, 68·4; H, 4·7. $C_{20}H_{16}O_6$ requires C, 68·2; H, 4·6%).

5 : 8 : 3″ : 4″-*Tetramethoxyfurano*(4′ : 5′ : 6 : 7)*flavone* (XIII; R and R_1 = OMe).—The *veratroate* (4 g.) from kellinone (3 g.) separated from methanol in colourless plates, m. p. 130° (Found: C, 63·2; H, 5·1. $C_{21}H_{20}O_8$ requires C, 63·0; H, 5·0%). A mixture of this ester (2·5 g.), sodamide (5 g.), and toluene (50 ml.) was heated on the steam-bath for 12 hours; after isolation from its sodio-derivative, the resulting *diketone* (XII; R = veratroyl) was purified from benzene–light petroleum (b. p. 60—80°), forming red prisms (1·0 g.), m. p. 125°, and giving an olive green ferric reaction in alcohol which changed to dark red in a few seconds (Found: C, 63·4; H, 5·1. $C_{21}H_{20}O_8$ requires C, 63·0; H, 5·0%).

Cyclisation of the foregoing diketone (0·5 g.) in boiling acetic acid (25 ml.) containing 3 drops of concentrated hydrochloric acid during 30 seconds gave rise to the *flavone* (XIII; R and R_1 = OMe) which was precipitated with water (100 ml.) and then recrystallised from methanol, forming flat yellow prisms (0·4 g.), m. p. 182°, moderately soluble in benzene or acetone and readily soluble in chloroform (Found: C, 65·7; H, 4·7. $C_{21}H_{18}O_7$ requires C, 65·9; H, 4·7%).

The authors are indebted to Messrs. Imperial Chemical Industries Limited for a grant in aid of this work.

UNIVERSITY OF LIVERPOOL. [*Received, March 11th,* 1948.]

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73. *Cyclic Meso-ionic Compounds. Part I. The Structure of the Sydnones and Related Compounds.*

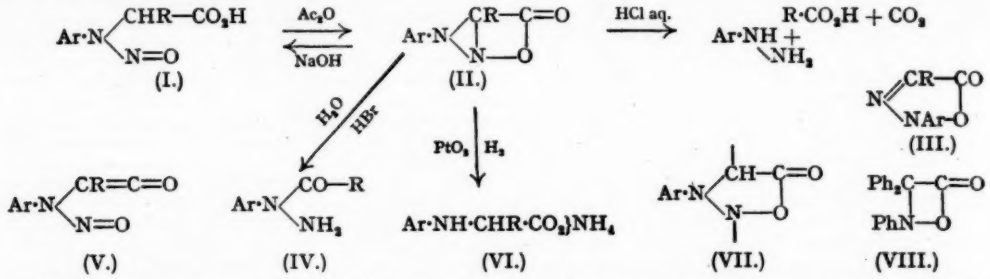
By WILSON BAKER, W. D. OLLIS, and V. D. POOLE.

The sydnones, obtained by dehydration of the *N*-nitroso-*N*-arylglycines (I) with acetic anhydride, have previously been given the improbable dicyclic structure (II). It is now shown in a detailed discussion that this formulation is inconsistent with the properties of these compounds. A modified hybrid structure of aromatic type is proposed, which is derived from a number of contributing ionic forms, some of which are shown in formulæ (IX—XXII). The term " meso-ionic " is suggested for compounds of this type. N-cyclo*Hexylsydnone* and N-*benzylsydnone* are typical sydnones, and the stability of the heterocyclic ring, therefore, does not depend upon union with an aromatic nucleus. A number of other new sydnones required for dipole moment investigation have been prepared. A brief review is given of some of the many molecules of this type which are known or may be capable of existence.

THE work of J. C. Earl and his collaborators has shown that the *N*-nitroso-*N*-arylglycines (I; R = H) readily lose a molecule of water when treated with acetic anhydride at room temperature to give unimolecular anhydro-compounds (Earl and Mackney, *J.*, 1935, 899; Eade and Earl, *J.*, 1946, 591). The reaction also occurred in the case of *N*-nitroso-α-anilinopropionic acid (I; R = Me; Ar = Ph), but not with *N*-nitroso-α-anilino*iso*butyric acid, $Ph{\cdot}N(NO){\cdot}CMe_2{\cdot}CO_2H$. As these anhydro-compounds had been prepared in the University of Sydney they were termed " sydnones ", the anhydro-derivative of *N*-nitroso-*N*-phenylglycine being referred to as *N*-phenylsydnone.

The sydnones were shown to be neutral, highly crystalline, stable compounds, fairly soluble (except *p*-nitrophenylsydnone) in most organic solvents including benzene. When hydrolysed with hot, dilute alkali they regenerated the *N*-nitroso-*N*-arylglycines, but hydrolysis with hot, concentrated hydrochloric acid gave one molecule each of an arylhydrazine and formic acid, carbon dioxide being also evolved. In the case of the sydnone derived from *N*-nitroso-α-anilinopropionic acid, acetic acid was produced in place of formic acid. The structure (II), the " lactone of 2-hydroxy-1-phenyldiaziridine-3-carboxylic acid ", was tentatively suggested for these compounds; it contains fused 3- and 4-membered rings, the latter being of the β-lactone type. This structure was regarded as incompletely satisfactory by two of us (Baker and Ollis, *Nature*, 1946, **158**, 703), and later by its proposers (Earl, *ibid.*, p. 909), but the evidence (*a*)

in favour of a structure related to (II), and (*b*) against certain details of this formulation, have not previously been set out.

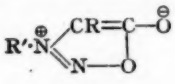


(*a*) The ready regeneration of the *N*-nitroso-*N*-arylglycines from the sydnones by alkaline hydrolysis shows that a very close relationship exists between the two compounds, and excludes the possibility that the sydnones might be represented by the simple five-membered ring formula (III), which would require a migration of the aryl group from nitrogen to nitrogen during the preparation of the sydnones, and the reverse migration during hydrolysis. Neither is likely to occur under the reaction conditions employed. No additional evidence of structure is provided by the production of an arylhydrazine by acid hydrolysis, but we have now established that this breakdown is a specific reaction of the sydnones and is not exhibited by the *N*-nitroso-*N*-arylglycines. Similarly, the interesting production of α-acylhydrazines (IV) by treatment of a sydnone in benzene solution with hydrogen bromide (Kenner and Mackay, *Nature*, 1947, **160**, 465) again gives no additional evidence of structure, nor does the observation now recorded in this paper that *N*-phenylsydnone can be reduced catalytically in presence of platinum oxide to give the ammonium salt of *N*-phenylglycine (VI; Ar = Ph, R = H). The sydnones do not show the Liebermann nitroso-reaction, and hence do not contain an *N*-nitroso-group, but the presence of a readily hydrolysable lactonic grouping is without doubt. The only conceivable alternative to a lactone is to regard the sydnones as *N*-nitroso-α-anilino-ketens (V), but this can be excluded because the sydnones do not possess a nitroso-group, and because they do not exhibit the properties characteristic of the ketens; they are, for example, stable towards boiling methyl and ethyl alcohols. Further, the nitroso-keten formula (V) cannot be a contributor to a hybrid structure containing the 5-membered ring (see below) shown in (II), as has been suggested by Earl, Leake, and Le Fèvre (*Nature*, 1947, **160**, 366), since the keten group $>C{=}C{=}O$ is linear (as is equally the polarised form $>\overset{\ominus}{C}{-}C{\equiv}\overset{\oplus}{O}$ also considered in this connection), whereas in any cyclic structure this grouping would of necessity be angular. The sydnones are soluble in hydrocarbons and cannot, therefore, possess a purely zwitterionic structure, and the evidence in favour of their possessing a heterocyclic 5-membered ring as in the formula (VII) is overwhelming.

(*b*) The reasons which render structure (II) unacceptable (Baker and Ollis, *loc. cit.*) are as follows. (1) A system possessing fused three- and four-membered rings would be highly strained, and unlikely to be produced by dehydration with acetic anhydride in the cold. β-Lactones of the ordinary type are not formed under these reaction conditions. (2) Many β-lactones are unstable to heat and readily lose carbon dioxide, and compound (VIII), which contains a four-membered β-lactone ring closely analogous to that present in structure (II), loses carbon dioxide spontaneously (Staudinger and Jelagin, *Ber.*, 1911, **44**, 365; quoted by Earl, *loc. cit.*). The sydnones do not decompose readily on being heated (for example, *N*-phenylsydnone can be sublimed unchanged at 110°/1 mm.), and are, therefore, unlikely to be β-lactones. The fact that some carbon dioxide is evolved and resinous products formed when *N*-phenylsydnone is boiled with water and a small amount of sodium carbonate or acetate is used by Earl as an argument supporting a β-lactone structure, but this evidence is unacceptable. Since acidic products are formed by the hydrolysis of the sydnones, the evolution of carbon dioxide from sodium carbonate solution is without significance, but we now find that carbon dioxide is also evolved when *N*-phenylsydnone is boiled with water and a little sodium borate. However, as *N*-nitroso-*N*-phenylglycine must be produced in the early alkaline stage of the experiments, later, when the solution becomes acid, its known decomposition into carbon dioxide and *N*-nitrosomethylaniline will occur (O. Fischer, *Ber.*, 1899, **32**, 249). These experiments throw no light on the chemical behaviour of the sydnone molecule. (3) If the sydnones were correctly represented by structure (II) they should be capable of existing in optically active

forms, even where R = H. Kenner and Mackay (*Nature*, 1946, **158**, 909) have prepared dextrorotatory *N*-nitroso-*N*-phenylalanine (I; R = Me; Ar = Ph) and find that it is converted by acetic anhydride into the optically inactive *N*-phenyl-*C*-methylsydnone (II; R = Me; Ar = Ph), and a similar loss of activity was recorded by Earl (*loc. cit.*) during the conversion of optically active *N*-nitroso-α-anilinophenylacetic acid (I; R = Ar = Ph) into *NC*-diphenylsydnone (II; R = Ar = Ph) (no m. p. or other details of this preparation are recorded). Whilst these experiments are of some significance, they do not rigidly exclude the possibility that sydnones might exist in optically active forms. (4) On the basis of structure (II) the benzene nucleus of *N*-phenylsydnone should undergo very ready substitution by cationoid reagents, as it may be regarded as a dialkylaniline, or more strictly an α-alkylphenylhydrazine. *N*-Phenylsydnone does, in fact, undergo bromination, but in the monobromo-derivative produced the bromine atom is linked to one of the carbon atoms of the sydnone ring (II; R = Br; Ar = Ph); no substitution occurs in the benzene nucleus (Kenner and Mackay, *Nature*, 1946, **158**, 909).

Some of the foregoing considerations led two of us (Baker and Ollis, *loc. cit.*) to put forward a modified five-membered ring structure for the sydnones which cannot be satisfactorily represented by any one purely covalent formula. This modification omits the bridge bond in (II) and substitutes a hybrid structure derived from a number of ionic states, some dipolar and some tetrapolar. Some of these contributing forms are shown in formulæ (IX—XXII). Of the eight dipolar forms, (IX) and (XII) are partly aromatic in character, and (X) and (XIII) also possess conjugated systems and may be expected to make important contributions to the hybrid. Of the four tetrapolar forms, (XVII) and (XVIII) both contain cyclic conjugated systems, and, in particular, (XVII) should contribute considerably to the whole hybrid. Formulæ are excluded which possess charges on adjacent atoms, except when one of the atoms is nitrogen in the quadricovalent state, or oxygen in the tercovalent state. In the formulæ, R = H, an alkyl or aryl group; R′ = an aryl or alkyl group.



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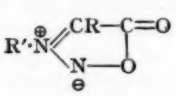

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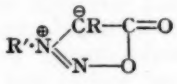

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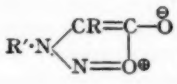

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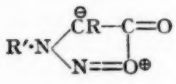

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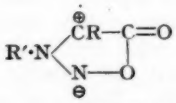

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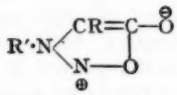

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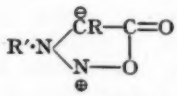

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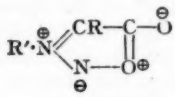

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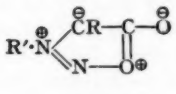

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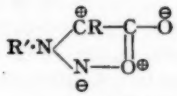

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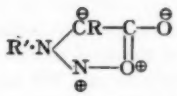
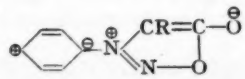
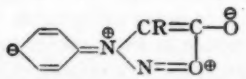


(XX.)

(XXI.)





(XXII.)

The bridged ring structure (II) is unlikely to make any effective contribution to the hybrid, as it would involve a much shorter distance between the CR group and the unsubstituted nitrogen atom than is possible in the above formulæ. In the case of the *N*-arylsydnones (R′ = aryl), many other possibilities of resonance occur involving the aryl nucleus; two of these are shown in formulæ (XXI) and (XXII) which are derived from (IX) and (XII). Further possible contributors to the hybrid are diradical types, but these are excluded from this discussion. The open-chain nitroso-keten type (V) has already been excluded on steric grounds. Examination of the formulæ (IX—XX) and, in particular, those [(IX), (X), (XII), (XIII), (XVII), (XVIII)] which may be expected to make considerable contributions to the hybrid, shows that although the dipoles of the different structures will be variously orientated so that the dipole of the sydnone molecule may be expected to be considerably less than that of a zwitterionic molecule with fixed charges, yet the substituted nitrogen atom will be expected to bear a large fractional positive charge, and the negative end of the sydnone dipole will be more diffusely directed towards the lactonic carbonyl grouping.

This general view of the structure of the sydnones has been fully supported by measurements of their dipole moments, preliminary mention of which has already been made (Baker, Ollis, Poole, Barltrop, Hill, and Sutton, *Nature*, 1947, **160**, 366; Earl, Leake, and Le Fèvre, *ibid.*, p. 366), and which will be the subject of a later paper. It also answers the objections to the bridged-ring structure and is consistent with the known facts of sydnone chemistry, requiring that the sydnones should (1) be virtually strainless and exhibit a general stability of aromatic type, (2) not show the properties of β-lactones, (3) possess planar molecules incapable of optical activity, (4) behave physically like molecules of fairly high dipole moment, (5) not contain a chemically reactive benzene nucleus, since the nitrogen atom directly attached to the benzene ring is approaching in character the nitrogen atom in an anilinium cation, $Ph–\overset{\oplus}{N}R_3$. The sydnones should possess appreciable resonance energy, and this is indicated by their difficulty of catalytic reduction, which is very slow even in the presence of platinum oxide. Their hybrid nature renders difficult the interpretation of their chemical reactions, and we feel it is unwise at this stage to attempt this either in terms of any one or more arbitrarily chosen contributing forms, or by analogy with the chemical behaviour of known compounds of essentially covalent character.

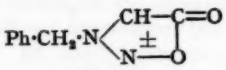
In discussing the ionic structures which contribute to the hybrid sydnone molecule, it was mentioned that forms such as (XXI) and (XXII) involving polarisation of the benzene nucleus might be involved. In order to see if such contributors were essential to the stability of the sydnone structure, the preparation of N-*benzylsydnone* (XXIII) and N-cyclo*hexylsydnone* (XXIV) was undertaken, and, as already reported (Baker, Ollis, Poole, Barltrop, Hill, and Sutton, *loc. cit.*) the syntheses proceeded normally. These two sydnones are similar to the *N*-arylsydnones in their physical properties and chemical behaviour. Contributing forms such as (XXI) and (XXII) involving polarisation of the benzene ring are, therefore, not essential for the existence of the sydnone ring. *N*-Benzylsydnone was smoothly hydrolysed by alkali to N-*nitroso*-N-*benzylglycine*, and hydrolysis with hydrochloric acid gave benzylhydrazine hydrochloride characterised as its α-nitroso-derivative and by the formation of p-*nitrobenzaldehyde benzylhydrazone*: *N-cyclo*Hexylsydnone behaved similarly, giving on alkaline hydrolysis *N*-nitroso-*N-cyclo*hexylglycine, and on acid hydrolysis *cyclo*hexylhydrazine hydrochloride.

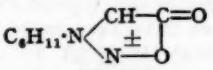
Further evidence in support of the proposed structure for the sydnones is provided by a study of their ultra-violet absorption spectra in alcoholic solution. *N-cyclo*Hexylsydnone (curve 1), which contains no possible conjugated system apart from the sydnone ring, shows a well-defined absorption band at 292 mμ, and *N*-benzylsydnone (curve 2) in which conjugation between the phenyl group and the sydnone nucleus is impossible, also shows absorption at exactly the same wave-length. This band at 292 mμ is therefore characteristic of the sydnone ring itself. If these two compounds had dicyclic covalent structures, as (II), they would not be expected to show strong absorption in this part of the spectrum. In *N*-phenylsydnone (curve 3), conjugation between the phenyl group and the heterocyclic nucleus causes a displacement of this band from 292 to 310 mμ, and a new band also appears at *ca.* 238 mμ owing to a similar shift of the ethylenic absorption of the benzene ring. *NC*-Diphenylsydnone (curve 4) shows a still greater displacement to 333 mμ of the absorption band characteristic of the sydnone ring, thus indicating increased conjugation. In this connection it is noteworthy that the three diaryl sydnones described in this paper all show a white fluoresence in ultra-violet light.

The sydnones are thus compounds exhibiting aromatic characteristics, which can be represented only as resonance hybrids of a large number of contributing ionic forms. It is impossible to represent them, even approximately, by any one covalent formula, or as a hybrid of a number of covalent formulæ, and their case is therefore fundamentally different from that of most organic compounds which can be satisfactorily represented either by a single covalent form, or as a hybrid of a few covalent forms, *e.g.*, benzene and naphthalene, or as a hybrid of covalent and ionic forms, *e.g.*, the amides. The closest analogies are provided by the aliphatic diazo-compounds, which can be represented only as hybrids of two zwitterionic forms $>C{=}\overset{\oplus}{N}{=}\overset{\ominus}{N}$ and $>\overset{\ominus}{C}{-}\overset{\oplus}{N}{\equiv}N$, and by the organic azides, which are similarly derived from the forms $R{-}N{=}\overset{\oplus}{N}{=}\overset{\ominus}{N}$ and $R{-}\overset{\ominus}{N}{-}\overset{\oplus}{N}{\equiv}N$ (see Taylor and Baker, Sidgwick's "Organic Chemistry of Nitrogen," 1942, pp. 362, 365). For molecules of this type we propose to use the adjective "meso-ionic", and the sydnones afford an example of cyclic meso-ionic compounds.

For cyclic meso-ionic structures it is necessary to have a simple symbol to give expression to the structural considerations discussed above, and it seems convenient to adopt the sign ± proposed by Simpson (*J.*, 1946, 95) for molecules like anthranil, piazthiole, 2-substituted ind-

azoles, and related types for which mainly meso-ionic structures had been previously proposed (Baker, *J.*, 1945, 267). *N*-Phenylsydnone is thus conveniently represented by formula (XXV).


(XXIII.)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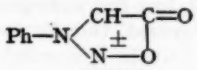
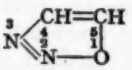
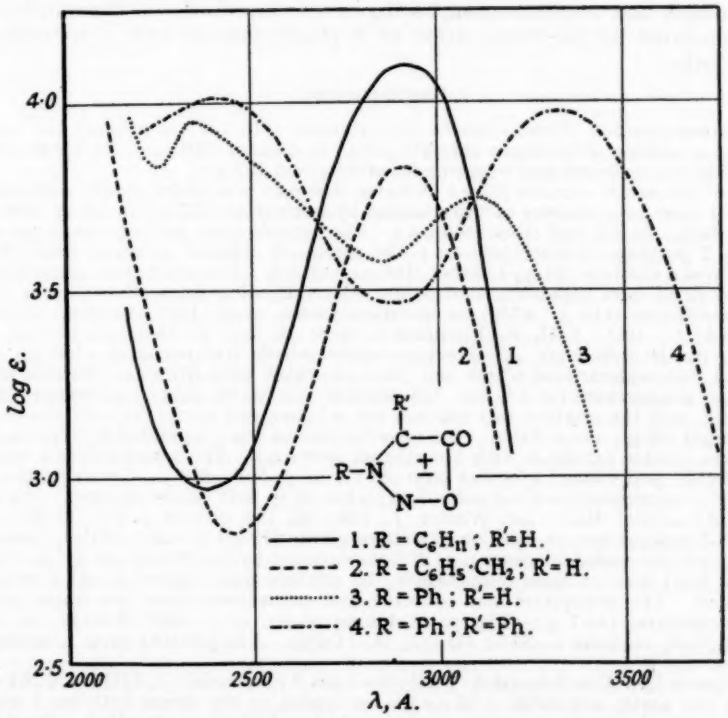
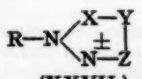

(XXV.)

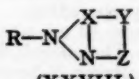

(XXVI.)

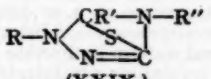
As will be indicated later, many cyclic meso-ionic compounds containing a heterocyclic 5-membered ring are possible. A number are, in fact, already described in the literature, and as the multiplication of trivial names is to be deprecated, it is necessary to adapt existing systematic nomenclature to substances of this type. *N*-Phenylsydnone (XXV) is a derivative of 1-oxa-2 : 3-diazole (XXVI), and structure (XXV) with its two unsatisfied valencies is 5-keto-3-phenyl-3 : 5-dihydro-1-oxa-2 : 3-diazole. It is suggested that this name should be prefixed by the symbol ψ to indicate the hybrid ionic structure of the compound, so that *N*-phenylsydnone becomes ψ-5-keto-3-phenyl-3 : 5-dihydro-1-oxa-2 : 3-diazole.

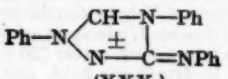


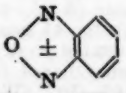
The sydnones form a special case of a group of related cyclic meso-ionic compounds which may be represented by the general formula (XXVII), where X = CH, CR, or N; Y–Z or Z–Y = –CO–O–, –NR–CO–, –NR–C(:NR')–, or –O–C(:NR)– or any of the related mono- or di-thio-

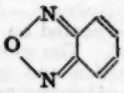

(XXVII.)


(XXVIII.)


(XXIX.)


(XXX.)


(XXXI.)


(XXXII.)

derivatives, R being an alkyl or aryl group throughout. Many compounds conforming to this type are to be found in the literature, but they have generally been regarded as bridged-ring compounds, *e.g.*, (XXVIII), or as the stereochemically unacceptable *endo*-oxy-, -thio-, or -imino-compounds, *e.g.*, (XXIX), which has been suggested as an alternative structure for the " *endo*-thiotriazolines ". The well-known reagent " nitron " is best represented by the formula (XXX)

instead of as an *endo*-anilo-compound (cf. XXIX). Schönberg appears to have been the first to suggest the possibility of hybrid, ionic, cyclic structures for certain triazoles including nitron (*J.*, 1938, 824), but the wide generality of this type of molecule does not appear to have been previously recognised, though the ideas have been more precisely formulated by Jensen and Friediger (*Kgl. Danske Videnskab. Selskab*, 1943, **20**, 1; see *Chem. Abs.*, 1945, **39**, 2068) as the result of dipole moment measurements. A further class of compounds belonging to the group represented by formula (XXVII) is where Y–Z or Z–Y is part of a benzene or aromatic nucleus, in which case R–N (in, for example, the 2-substituted-indazoles or -benztriazoles) may be replaced by O, as in benzfurazan (XXXI), S, as in piazthiole and Se, as in piaselenole. In these cases, which have already received slight general consideration (Baker, *J.*, 1945, 258), the possibility exists that covalent *o*-quinonoid forms (as XXXII) may make a large contribution to the hybrid molecule.

A number of sydnones have been prepared for measurement of their dipole moments to be discussed in Part II of this series. These are N-p-*tolyl*, N-p-*chlorophenyl*-, NC-*diphenyl*-, C-*phenyl*-N-p-*chlorophenyl*-, and C-*phenyl*-N-p-*tolyl*-*sydnone*. Improved preparations of *C*-bromo-*N*-phenyl- and *N*-*p*-nitrophenyl-sydnone are described. *C*-Bromo-*N*-phenylsydnone can also be prepared by the bromination of *N*-phenylsydnone with *N*-bromosuccinimide in chloroform solution.

Experimental.

N-*Benzylaminoacetonitrile Hydrochloride*.—Benzylamine (110 c.c.) in ethanol (50 c.c.) was added with shaking to a solution of hydrogen chloride (40 g.) in ethanol (200 c.c.). After standing overnight the hydrochloride was collected and washed with ether (yield 137 g.).

A solution of potassium cyanide (63 g.) in water (150 c.c.) was added slowly with stirring and ice-cooling during 1 hour to a mixture of benzylamine hydrochloride (137 g.) in water (300 c.c.), aqueous formaldehyde (35%; 82 g.), and ether (500 c.c.). The organic layer was separated, the aqueous layer extracted with 3 portions of ether (250 c.c.), the combined ethereal solutions dried ($MgSO_4$), and a solution of hydrogen chloride (50 g.) in ether (150 c.c.) added. The crystalline precipitate was washed with ether and dried over potassium hydroxide. Crystallisation from ethanol gave N-*benzylaminoacetonitrile hydrochloride* (114 g.; 65%) as colourless plates, m. p. 171° (decomp.) (Found: C, 58·6; H, 6·2; N, 15·3; Cl, 19·5. $C_9H_{11}N_2Cl$ requires C, 59·2; H, 6·0; N, 15·3; Cl, 19·5%).

N-*Benzylglycine Hydrochloride*.—*N*-Benzylaminoacetonitrile hydrochloride (100 g.) was dissolved in concentrated hydrochloric acid which had been saturated with hydrogen chloride at 0° (350 c.c.) and left at room temperature for 1 hour. On dilution with water (250 c.c.) crystals, probably of the amide, separated, and the mixture was refluxed for 4 hours, left overnight, and the colourless plates collected and dried (88 g.; m. p. 205°). The aqueous filtrate was evaporated to dryness under reduced pressure, and the residue extracted with hot ethanol (500 c.c.). The cooled solution was filtered from ammonium chloride, and yielded a further crop (25 g.; m. p. 195—200°). Crystallisation from ethanol gave *N*-benzylglycine hydrochloride as colourless plates, m. p. 220° (slight decomp.) (the m. p. depends upon the rate of heating; Mason and Winder, *J.*, 1894, **65**, 190, give m. p. 214—215°).

N-*Nitroso*-N-*benzylglycine*.—A solution of sodium nitrite (19 g.) in water (60 c.c.) was added during 1 hour to a stirred, ice-cooled suspension of *N*-benzylglycine hydrochloride (50 g.) in water (200 c.c.). After being left for 1 hour at room temperature, the mixture was acidified to pH 4 with concentrated hydrochloric acid. The precipitate was collected and crystallised from hot water (*ca.* 1 l.) giving N-*nitroso*-N-*benzylglycine* (41·7 g.; 87%) as glistening plates, m. p. 148° (Found: C, 55·6; H, 5·4; N, 14·3. $C_9H_{10}O_3N_2$ requires C, 55·7; H, 5·2; N, 14·4%). The product gives a strong Liebermann nitroso-reaction.

N-*Benzylsydnone* (*ψ*-5-*Keto*-3-*benzyl*-3 : 5-*dihydro*-1-*oxa*-2 : 3-*diazole*) (XXIII).—*N*-Nitroso-*N*-benzylglycine (40 g.) and acetic anhydride (185 c.c.) were heated on the steam-bath for 5 hours, and then distilled under reduced pressure leaving a residue which solidified on standing. Crystallisation from benzene–light petroleum (b. p. 40—60°) gave colourless plates, m. p. 67°. Further recrystallisation gave pure N-*benzylsydnone* as colourless plates, m. p. 69·5° [Found: C, 61·2; H, 5·0; N, 15·9; *M* (Rast), 174. $C_9H_8O_2N_2$ requires C, 61·4; H, 4·6; N, 15·9%; *M*, 176]. It is insoluble in aqueous sodium carbonate and does not give Liebermann's nitroso-reaction. Earl, Leake, and Le Fèvre (*loc. cit.*) mentioned *N*-benzylsydnone, but gave no m. p. or details of preparation.

Alkaline Hydrolysis of N-*Benzylsydnone*.—*N*-Benzylsydnone (2 g.) was heated on the steam-bath for 3 hours with water (20 c.c.) and sodium hydroxide (1 g.). The cooled, filtered solution was acidified with hydrochloric acid, and the crystalline precipitate of *N*-nitroso-*N*-benzylglycine was collected and dried (2·05 g.; 93%), m. p. 144°, mixed m. p. 146°.

Acid Hydrolysis of N-*Benzylsydnone*.—*N*-Benzylsydnone (5 g.), water (50 c.c.), and concentrated hydrochloric acid (25 c.c.) were heated on the steam-bath for 4½ hours; solution gradually occurred, and carbon dioxide was evolved. The solution was evaporated to dryness, and the residue dried in a vacuum over potassium hydroxide and crystallised from ethanol (20 c.c.), giving benzylhydrazine monohydrochloride (2·65 g.) as colourless needles, m. p. 105—107° (Wohl and Oesterlin, *Ber.*, 1900, **33**, 2739, give m. p. 110°). Treatment of this benzylhydrazine hydrochloride (500 mg.) in water (3 c.c.) with sodium nitrite (250 mg.) gave a solid (230 mg.; 49%), crystallisation of which from benzene–light petroleum (b. p. 40—60°) gave *α*-*N*-nitrosobenzylhydrazine as colourless needles, m. p. 71° (Wohl and Oesterlin, *loc. cit.*, give m. p. 71°). The benzylhydrazine hydrochloride also readily gave *p*-*nitrobenzaldehyde benzylhydrazone* as yellow needles from ethanol, m. p. 131° (decomp.) (Found: C, 65·7; H, 5·1; N, 16·7. $C_{14}H_{13}O_2N_3$ requires C, 65·9; H, 5·1; N, 16·5%).

N-*Nitroso*-N-cyclo*hexylglycine*.—*cyclo*Hexylglycine hydrochloride was prepared from *cyclo*hexylamine hydrochloride (40 g.) by the Strecker synthesis (Zelinsky and Arzibacheff, *Ber.*, 1907, **40**, 3054), and was purified by dissolution in alcohol and precipitation of the accompanying ammonium chloride with ether. After removal of the solvents, the *N-cyclo*hexylglycine hydrochloride was dissolved in water (200 c.c.), and a solution of sodium nitrite (20 g.) in water (40 c.c.) was added dropwise during 30 minutes with stirring and ice-cooling. After 2 hours the solution was acidified, and the solid collected and crystallised from hot water, giving *N*-nitroso-*N-cyclo*hexylglycine (30 g.) as colourless needles, m. p. 117° [Zelinsky and Arzibacheff, *loc. cit.*, give m. p. 117·5—118° (decomp.)].

N-cyclo*Hexylsydnone* (*ψ-5-Keto*-3-cyclo*hexyl*-3 : 5-*dihydro*-1-*oxa*-2 : 3-*diazole*) (XXIV).—*N*-Nitroso-*N-cyclo*hexylglycine (30 g.) was dissolved in acetic anhydride (200 c.c.) and left at room temperature in the dark for 3 days. Excess of acetic anhydride was removed under reduced pressure and the solid residue was recrystallised thrice from benzene–light petroleum (b. p. 60—80°), giving N-cyclo*hexylsydnone* (17 g.; 63%) as colourless, flat needles, m. p. 64° [Found: C, 57·4; H, 7·3; N, 16·6; *M* (Rast), 165. $C_8H_{12}O_2N_2$ requires C, 57·2; H, 7·2; N, 16·7%; *M*, 168]. The product is insoluble in aqueous sodium carbonate and gives no reaction for a nitroso-group. Slight decomposition is observed after long periods.

Acid Hydrolysis of N-cyclo*Hexylsydnone*.—*N-cyclo*Hexylsydnone (2 g.) was heated on a steam-bath with water (3 c.c.), alcohol (3 c.c.), and concentrated hydrochloric acid (10 c.c.) for ½ hour, carbon dioxide being evolved. The solution was taken to dryness, and formic acid was detected in the distillate. The residue of *cyclo*hexylhydrazine hydrochloride had m. p. 111° (Harkins and Lochte, *J. Amer. Chem. Soc.*, 1924, **46**, 454, give m. p. 107—110°), and was characterised, by the addition of phenyl *iso*thiocyanate, as the phenylthiosemicarbazide, m. p. 146° from alcohol (Kizhner and Byelov, *J. Russ. Phys. Chem. Soc.*, 1911, **43**, 577, see *Chem. Abs.*, 1912, **6**, 347, give m. p. 143°; Harkins and Lochte, *loc. cit.*, give m. p. 148°). It was also converted into the condensation product with benzaldehyde, m. p. 183° from ethyl acetate (Harkins and Lochte record the same m. p.), the structure of which has not been established.

Alkaline Hydrolysis of N-cyclo*Hexylsydnone*.—*N-cyclo*Hexylsydnone (0·5 g.) was refluxed with 2N-sodium hydroxide (10 c.c.) for ½ hour, and the solution then filtered and acidified, precipitating *N*-nitroso-*N-cyclo*hexylglycine, m. p. and mixed m. p. 119°.

Catalytic Reduction of N-*Phenylsydnone*.—*N*-Phenylsydnone (0·5 g.) in ethanol (100 c.c.) was shaken in hydrogen in presence of Adams's platinum oxide catalyst (0·1 g.) till hydrogen uptake (230 c.c.; $3H_2$ requires 220 c.c.) ceased (3 hours). Evaporation of the filtered solution left a residue (0·46 g.) which when treated with alcoholic potassium hydroxide evolved ammonia and deposited the potassium salt of *N*-phenylglycine. The free acid after crystallisation from light petroleum (b. p. 100—120°) had m. p. 123°, and was converted into *N*-nitroso-*N*-phenylglycine, m. p. and mixed m. p. 104°.

C-Bromo-N-*phenylsydnone* (*ψ-4-Bromo-5-keto*-3-*phenyl*-3 : 5-*dihydro*-1-*oxa*-2 : 3-*diazole*).—(*a*) The action of bromine on *N*-phenylsydnone in acetic acid to give a bromo-derivative, m. p. 134°, has been noted by Kenner and Mackay (*Nature*, 1946, **158**, 910); we find that the reaction takes place more smoothly in acetic anhydride solution, and the formation of violet by-products is avoided.

A solution of bromine (10 g.) in acetic anhydride (25 c.c.) was added at 0° to a suspension of *N*-phenylsydnone (10 g.) in acetic anhydride (100 c.c.), and after a short time a light yellow solid had separated. The residue (12·6 g.) left after the removal of the solvents under diminished pressure was crystallised from ethanol, giving *C*-bromo-*N*-phenylsydnone (12·1 g.; 81%) as colourless needles, m. p. 140° (decomp.) (Found: C, 39·7; H, 2·1; N, 11·8; Br, 33·2. Calc. for $C_8H_5O_2N_2Br$: C, 39·8; H, 2·1; N, 11·6; Br, 33·2%).

(*b*) *N*-Phenylsydnone (1 g.) dissolved in chloroform (10 c.c.) was refluxed for ½ hour with excess of *N*-bromosuccinimide (1·3 g.). The cooled mixture was filtered and evaporated, and the residue crystallised from alcohol, giving white needles (1 g.), m. p. 136°, undepressed when mixed with *C*-bromo-*N*-phenylsydnone prepared by the previous method.

N-p-*Tolylsydnone* (*ψ-5-Keto*-3-p-*tolyl*-3 : 5-*dihydro*-1-*oxa*-2 : 3-*diazole*).—A solution of *N*-nitroso-*N-p*-tolylglycine (prepared according to the directions of Vorländer and von Schilling, *Ber.*, 1901, **34**, 1646, for the *o*-tolyl isomer) (24 g.) in acetic anhydride (100 c.c.) was kept at room temperature for 48 hours and then poured into water. The *product*, after collection, crystallised from dilute ethanol in needles (8 g.), m. p. 142—144°. Further crystallisation from benzene gave long, lustrous, colourless needles, m. p. 144—145° (Found: C, 61·6; H, 4·6; N, 16·1. $C_9H_8O_2N_2$ requires C, 61·3; H, 4·5; N, 15·9%).

N-p-*Chlorophenylglycine Ethyl Ester*.—A mixture of ethyl chloroacetate (62 g.), *p*-chloroaniline (64 g.), ethanol (50 c.c.), and hydrated sodium acetate (60 g.) was refluxed (oil-bath at 125°) for 5 hours. Water (200 c.c.) was then added and the precipitated solid ester collected and washed. A further quantity of the ester was obtained by shaking the filtrate and washings with ether at pH 4, then neutralising and extracting with ether again, drying, and removing the ether from the second extract. The combined yields of ester were crystallised from ethanol, giving N-p-*chlorophenylglycine ethyl ester* (81 g.; 80%) as colourless plates, m. p. 88° (Found: C, 56·4; H, 5·5; N, 6·8. $C_{10}H_{12}O_2NCl$ requires C, 56·3; H, 5·6; N, 6·6%).

N-p-*Chlorophenylglycine*.—The preceding ester (53 g.), ethanol (20 c.c.), and a solution of sodium hydroxide (15 g.) in water (200 c.c.) were refluxed for ½ hour, filtered, and neutralised with concentrated hydrochloric acid (45 c.c.), and the precipitated acid collected and dried over potassium hydroxide (yield 45·5 g.; 98%). The m. p. of this material was 141° (Swalbe, Schulz, and Jochheim, *Ber.*, 1908, **41**, 3794, who prepared this acid by the Strecker reaction, give m. p. 141°).

N-*Nitroso*-N-p-*chlorophenylglycine*.—The above acid (40 g.) was suspended in water (400 c.c.), and a solution of sodium nitrite (16 g.) in water (60 c.c.) was added slowly at 0°. After 2 hours, when solution was complete, concentrated hydrochloric acid (25 c.c.) was added, and the solid nitroso-compound collected and dried over potassium hydroxide (yield, 46 g.). Recrystallisation from chloroform gave the rather unstable *N*-nitroso-*N-p*-chlorophenylglycine as almost colourless needles, m. p. 114°.

N-p-*Chlorophenylsydnone* (*ψ-5-Keto*-3-p-*chlorophenyl*-3 : 5-*dihydro*-1-*oxa*-2 : 3-*diazole*).—*N*-Nitroso-*N-p*-chlorophenylglycine (10 g.) and acetic anhydride (50 c.c.) were heated on the steam-bath for 90

minutes and distilled to dryness under diminished pressure, and the residue immediately crystallised from benzene–light petroleum (b. p. 60—80°), giving N-p-*chlorophenylsydnone* (8·2 g.; 82%) as light-yellow needles, m. p. 113° (Found: C, 49·1; H, 2·8; N, 14·1. $C_8H_5O_2N_2Cl$ requires C, 48·8; H, 2·6; N, 14·3%). The compound is insoluble in sodium carbonate solution, and gives no reaction for a nitroso-group. Hydrolysis with hydrochloric acid gave carbon dioxide and *p*-chlorophenylhydrazine characterised by conversion into benzaldehyde *p*-chlorophenylhydrazone, m. p. 127° (lit., m. p. 127°) and the *p*-chlorophenylhydrazone of pyruvic acid, m. p. 199° (Found: C, 50·6; H, 4·5. Calc. for $C_9H_9O_2N_2Cl$: C, 50·7; H, 4·2%) (Hewitt, *J.*, 1893, **63**, 873, gives m. p. 199°).

Ethyl α-Bromophenylacetate.—Phenylacetyl chloride (191 g.; b. p. 98°/14 mm.) was prepared by refluxing phenylacetic acid (200 g.), thionyl chloride (200 g.), and pyridine (1 c.c.) for 3 hours and then fractionating. To this acid chloride was added anhydrous bromine (217 g.) with stirring and irradiation with ultra-violet light during 1 hour, the temperature being then gradually raised to 60° where it was maintained for ½ hour. The resulting crude bromo-acid chloride was then carefully added to absolute ethanol (500 c.c.), excess of ethanol distilled off after standing overnight, and the ester dissolved in ether (500 c.c.), washed with aqueous sodium carbonate, dried, and distilled, finally giving ethyl α-bromophenylacetate (203 g.; 68%, b. p. 102—104°/1·5 mm., 146—150°/12 mm.) (cf. Anschutz, *Annalen*, 1907, **354**, 127, who records b. p. 150—152°/13 mm.).

α-Anilinophenylacetic Acid.—Ethyl α-bromophenylacetate (50 g.), aniline (19 c.c.), hydrated sodium acetate (28 g.), and ethanol (20 c.c.) were refluxed for 5 hours. After 12 hours the solid was triturated with 2N-sodium carbonate, washed with water, dried, and crystallised from light petroleum (b. p. 60—80°), giving ethyl α-anilinophenylacetate (46 g.; 86%) as needles, m. p. 87·5° (Bischoff, *Ber.*, 1897, **30**, 2305, gives m. p. 85°; Hinze, *Ber.*, 1899, **32**, 3056, m. p. 89—90°). Hydrolysis with 10% sodium hydroxide in presence of a little ethanol and precipitation at pH 4 gave α-anilinophenylacetic acid in quantitative yield, m. p. 183° (decomp.); after crystallisation from ethanol it had m. p. 185° (Hinze, *loc. cit.*, gives m. p. 183°, decomp.).

NC-*Diphenylsydnone* (*ψ-5-Keto-3 : 4-diphenyl-3 : 5-dihydro-1-oxa-2 : 3-diazole*).—Sodium nitrite (8·4 g.) was added with stirring to a solution of α-anilinophenylacetic acid (25 g.) in concentrated sulphuric acid (300 c.c.) at 0°, and after 1½ hours the mixture was poured on ice. The crude nitroso-acid was collected, washed, and heated on the steam-bath for 1 hour with acetic anhydride (90 c.c.), and cooled, water was added, and the solid was collected, washed with aqueous sodium carbonate, water, and alcohol, and dried. Crystallisation from ethanol (700 c.c.) gave NC-*diphenylsydnone* (15·5 g.) as light-yellow, thick, rhombic plates, m. p. 184·5° (Found: C, 70·7; H, 4·5; N, 11·6. $C_{14}H_{10}O_2N_2$ requires C, 70·6; H, 4·2; N, 11·8%). It is insoluble in aqueous sodium carbonate, gives no reaction for a nitroso-group, and shows a white fluorescence in ultra-violet light.

α-p-*Chloroanilinophenylacetic Acid.*—Ethyl α-*p*-chloroanilinophenylacetate was prepared by the method used for ethyl α-anilinophenylacetate; it formed needles from light petroleum (b. p. 60—80°), m. p. 88·5° (84% yield) (Bischoff, *Ber.*, 1897, **30**, 2763, records m. p. 87·8°). Alkaline hydrolysis gave α-p-*chloroanilinophenylacetic acid* (97% yield) as small, colourless needles from aqueous ethanol, m. p. 175° (decomp.) (Found: C, 63·9; H, 4·5; N, 5·5; Cl, 14·2. $C_{14}H_{12}O_2NCl$ requires C, 64·2; H, 4·6; N, 5·4; Cl, 13·6%).

C-*Phenyl*-N-p-*chlorophenylsydnone* (*ψ-5-Keto-4-phenyl-3-p-chlorophenyl-3 : 5-dihydro-1-oxa-2 : 3-diazole*).—Nitrosation of the preceding acid (15 g.) in concentrated sulphuric acid (300 c.c.) with sodium nitrite (4·5 g.), isolation of the crude nitroso-derivative, and conversion of it into the sydnone were carried out as in the case of *NC*-diphenylsydnone. C-*Phenyl*-N-p-*chlorophenylsydnone* (10·5 g.) was obtained by crystallisation from ethanol (50 c.c.) as thick, light-yellow plates, m. p. 124° (Found: C, 61·8 H, 3·4; N, 10·3; Cl, 13·4. $C_{14}H_9O_2N_2Cl$ requires C, 61·7; H, 3·3; N, 10·3; Cl, 13·0%).

C-*Phenyl*-N-p-*tolylsydnone* (*ψ-5-Keto-4-phenyl-3-p-tolyl-3 : 5-dihydro-1-oxa-2 : 3-diazole*).—This sydnone was prepared *via* ethyl α-*p*-toluidinophenylacetate (needles, m. p. 91·5° from light petroleum, b. p. 60—80°, yield 89%; Stockenius, *Jahresber.*, 1878, 781, gives m. p. 89—90°), α-*p*-toluidinophenylacetic acid (crystalline powder, m. p. 182°, decomp., from ethanol; yield 95%; von Miller and Plöchl, *Ber.*, 1896, **29**, 1739, give m. p. 178—182°, decomp.), and the nitroso-acid, prepared from α-*p*-toluidinophenylacetic acid (25 g.), concentrated sulphuric acid (250 c.c.), and sodium nitrite (7·9 g.). C-*Phenyl*-N-p-*tolylsydnone* was obtained in 64% yield from *N*-nitroso-α-*p*-toluidinophenylacetic acid as colourless needles from ethanol, m. p. 151° (Found: C, 71·5; H, 4·9; N, 11·2. $C_{15}H_{12}O_2N_2$ requires C, 71·4; H, 4·4; N, 11·1%).

N-p-*Nitrophenylsydnone* (*ψ-5-Keto-3-p-nitrophenyl-3 : 5-dihydro-1-oxa-2 : 3-diazole*).—Difficulty was experienced in nitrosating *N*-*p*-nitrophenylglycine in 36N-sulphuric acid (Eade and Earl, *loc. cit.*), but the reaction proceeds readily, and in somewhat greater yield than that claimed, in hydrochloric acid. A solution of sodium nitrite (7·7 g.) in water (25 c.c.) was added dropwise during ½ hour to a stirred, ice-cooled solution of *N*-*p*-nitrophenylglycine (20 g.) in concentrated hydrochloric acid (200 c.c.). After a total of 2 hours the nitroso-derivative was collected, washed, and dried; it crystallised from dilute ethanol in fine, light-yellow needles (21·5 g.; 93%), m. p. 149° (decomp.) (Eade and Earl record m. p. 147·5°, decomp.). Eade and Earl converted the nitroso-acid into *N*-*p*-nitrophenylsydnone by treatment with acetic anhydride at room temperature for 14 days, but an equally good yield is obtained by heating the acid with 5 times its weight of acetic anhydride for 2 hours on the steam-bath, and isolating the sydnone as previously described. It had m. p. 184° (Eade and Earl give m. p. 187—188°).

The authors' thanks are due to Dr. A. E. Gillam for a determination of the ultra-violet absorption spectrum of *N*-phenylsydnone, to Dr. J. A. Barltrop for details of the preparation of *N*-*p*-tolylsydnone, to Imperial Chemical Industries Limited for a grant and for a supply of *N*-phenylglycine, and to the Department of Scientific and Industrial Research for a maintenance allowance awarded to one of them (V. D. P.).

THE UNIVERSITY, BRISTOL. [*Received, March 30th*, 1948.]

74. *Alicyclic Glycols. Part I. Toluene*-p-*sulphonyl and Methanesulphonyl Derivatives of* cyclo*Hexane*-1 : 2-*diol.*

By M. F. Clarke and L. N. Owen.

The *monotoluene*-p-*sulphonates* and *monomethanesulphonates* of *cis*- and *trans-cyclo*hexane-1 : 2-diol have been prepared. The *trans*-compounds are very much more reactive than the *cis*-, and with alkali, sodium iodide, or lithium chloride, give *cyclo*hexene oxide, *trans*-2-iod*ocyclo*hexanol, or *trans*-2-chloro*cyclo*hexanol, respectively. The *cis*-compounds, with alkali, give *cyclo*hexanone, and, with the aqueous reagent, *cis-cyclo*hexane-1 : 2-diol, and react only slowly with sodium iodide or lithium chloride. Replacement of the sulphonyloxy-group in the *trans*-series results in overall retention of configuration, probably as a result of two successive inversions, whilst in the *cis*-series, where formation of an intermediate cyclic compound is less likely, a single inversion of configuration occurs. The reactions are compared with those involving replacement of toluene-*p*-sulphonyl groups in the carbohydrate field.

Simple esters of sulphonic acids, such as the alkyl toluene-*p*-sulphonates, on treatment with alcoholic alkali or alkoxide, usually give ethers :

$$R{\cdot}O{\cdot}Ts + R'{\cdot}ONa \longrightarrow R{\cdot}O{\cdot}R' + Ts{\cdot}ONa \ (Ts = p\text{-}CH_3{\cdot}C_6H_4{\cdot}SO_2)$$

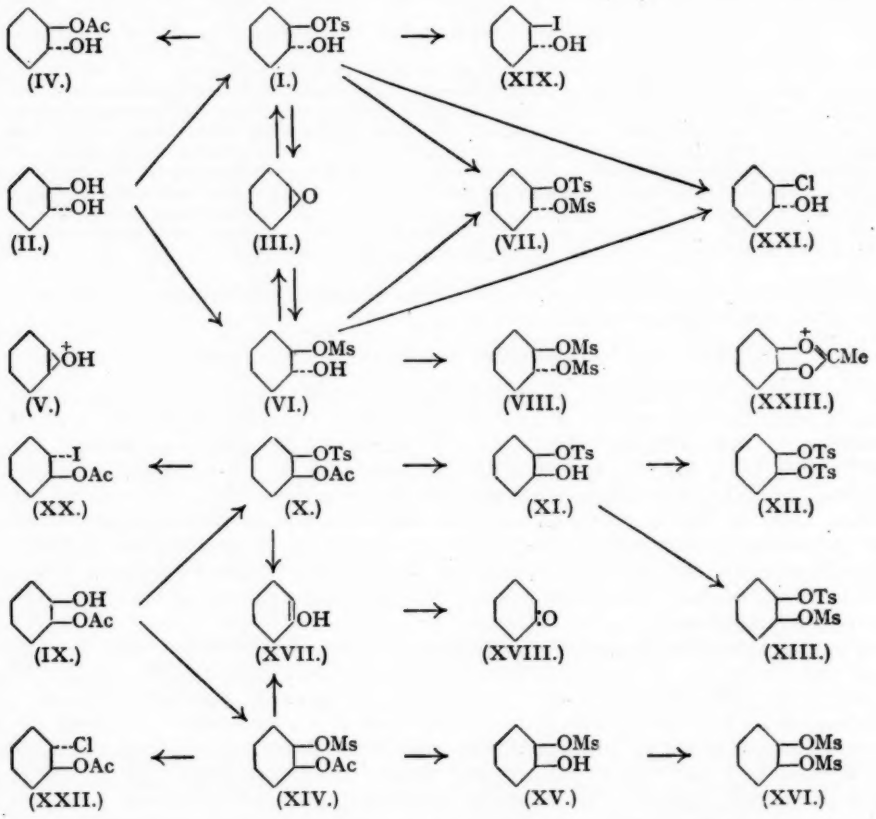
although olefins also are sometimes formed, by intramolecular loss of toluene-*p*-sulphonic acid, particularly when the derivative is of a secondary alcohol (Ferns and Lapworth, *J.*, 1912, **101**, 273; Phillips, *J.*, 1923, **123**, 44). In the alicyclic series, Hückel and his co-workers (*Annalen*, 1930, **477**, 143; 1937, **533**, 1) have studied the behaviour of a few simple monotoluene-*p*-sulphonates. *cyclo*Hexyl toluene-*p*-sulphonate, for example, gave only *cyclo*hexene when treated with dilute acids or alkalis, or with sodium acetate, the tendency towards olefin-formation entirely preventing substitution. The toluene-*p*-sulphonates of menthol and β-decalol also gave considerable amounts of the corresponding olefins, menth-3-ene and octalin respectively, when boiled with alcoholic potassium acetate, though small amounts of the ethyl ethers and acetates were also produced.

With monotoluene-*p*-sulphonates of polyhydroxy-compounds it is clear that the formation of ethers can also occur by intramolecular reaction, to yield anhydro-derivatives containing oxide rings; the α-toluene-*p*-sulphonate of glycerol, for example, on treatment with sodium methoxide gives 2 : 3-epoxypropanol (Fischer and Sowden, *J. Amer. Chem. Soc.*, 1942, **64**, 1291). if, however, the polyhydroxy-compound is cyclic, the stereochemical disposition of the toluene-*p*-sulphonyl group with reference to the hydroxyl group will evidently influence the tendency for such oxide-formation to occur. In the carbohydrate field, in which very extensive investigations of this nature have been carried out (cf. Peat, " Advances in Carbohydrate Chemistry ", Vol. II, p. 38) it has been firmly established that the formation of a 1 : 2-anhydro-ring is accompanied by inversion of configuration at the carbon atom originally carrying the toluene-*p*-sulphonyl group; consequently, for anhydro-ring formation of this type to occur it is necessary that there should be a *trans*-disposition between the toluene-*p*-sulphonyl and the adjacent hydroxyl (or potential hydroxyl) group. If this condition is not satisfied, then (unless some other type of oxide-ring formation is possible) the toluene-*p*-sulphonyl group is usually very resistant towards alkaline reagents, though under vigorous conditions it may undergo hydrolysis or ammonolysis without inversion.

Comparatively little is yet known about the behaviour of esters of methanesulphonic acid under similar conditions, but from the evidence so far available it appears that the above conclusions apply also to the methanesulphonyl derivatives of carbohydrates.

There is practically no information about the behaviour of analogous toluene-*p*-sulphonyl and methanesulphonyl derivatives of polyhydroxy-alicyclic compounds. Amongst the simple alicyclic diols, only one monotoluene-*p*-sulphonate (I) has been described. This was obtained by Criegee and Stanger (*Ber.*, 1936, **69**, 2753) by partial toluene-*p*-sulphonation of *trans-cyclo*hexane-1 : 2-diol (II) and also by scission of *cyclo*hexene oxide (III) with toluene-*p*-sulphonic acid, a reaction accompanied by the expected inversion; their attempts to prepare the *cis*-monotoluene-*p*-sulphonate from the *cis*-diol were unsuccessful. On treatment of the *trans*-monotoluene-*p*-sulphonate (I) with potassium acetate in methanol, they obtained the *trans*-monoacetate (IV), and since a direct replacement of toluene-*p*-sulphonyl by acetyl would be expected to give the *cis*-monoacetate, by a single inversion, they postulated the intermediate formation of *cyclo*hexene oxide (III), which with the liberated acetic acid was supposed to undergo the usual ring-opening to give the *trans*-monoacetate; an appreciable amount of the oxide was in fact detected in the reaction mixture. The more recent papers by Winstein and his co-workers

(*J. Amer. Chem. Soc.*, 1942, **64**, 2780, 2787, 2791, 2792, 2796; 1943, **65**, 613, 2196) have dealt in considerable detail with the influence of a neighbouring *trans*-group on reactivity, and have



provided a comprehensive explanation for the inversion or non-inversion accompanying the replacement of a group in such compounds under various conditions. The results observed by Criegee and Stanger can thus be explained by postulating the intermediate formation of (V), rather than of *cyclo*hexene oxide itself. It was nevertheless probable that the *trans*-monotoluene-*p*-sulphonate could be converted into the oxide under appropriate conditions, and, as part of a general investigation on alicyclic diols, we have prepared the *cis*- and *trans*-forms of the monotoluene-*p*-sulphonyl and of the monomethanesulphonyl derivatives of *cyclo*hexane-1 : 2-diol, and have studied their properties.

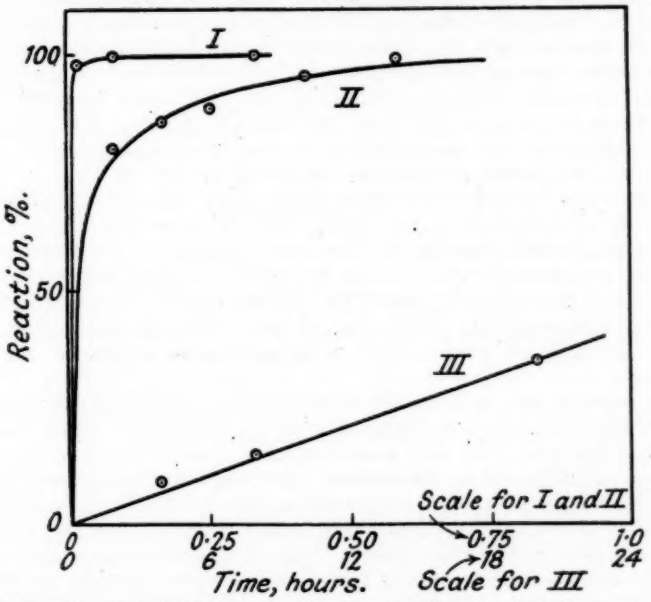
The trans-***monomethanesulphonate*** (VI) was obtained in high yield by reaction of methanesulphonic acid with *cyclo*hexene oxide, the ring-opening being accompanied by the expected inversion. The product was identical with that isolated, in poor yield, by the action of 1 mol. of methanesulphonyl chloride on the *trans*-diol in pyridine solution, and with toluene-*p*-sulphonyl chloride it gave the trans-*toluene*-p-*sulphonate-methanesulphonate* (VII), also obtained by methanesulphonation of the known *trans*-monotoluene-*p*-sulphonate (I). With excess of methanesulphonyl chloride, the *trans*-diol gave the trans-*bismethanesulphonate* (VIII).

The bistoluene-*p*-sulphonate of *cis-cyclo*hexane-1 : 2-diol has already been described by Criegee and Stanger (*loc. cit.*), who reported that this diol, unlike the *trans*-isomer, could not be converted into a monotoluene-*p*-sulphonate by the use of 1 mol. of toluene-*p*-sulphonyl chloride. We have now succeeded in preparing this mono-derivative by an indirect route from the *cis*-monoacetate (IX), which on toluene-*p*-sulphonation yielded the cis-*toluene*-p-*sulphonate-acetate* (X). When this was treated with cold methanolic hydrogen chloride it was smoothly deacetylated to give the cis-*monotoluene*-p-*sulphonate* (XI) as a liquid, characterised by conversion into the *cis*-bistoluene-*p*-sulphonate (XII) and also by methanesulphonation to give the cis-*toluene*-p-*sulphonate-methanesulphonate* (XIII). Similarly, methanesulphonation of the *cis*-monoacetate

(IX) gave the cis-*methanesulphonate-acetate* (XIV), and thence, by deacetylation, the cis-*monomethanesulphonate* (XV); this was characterised by conversion into the cis-*bismethanesulphonate* (XVI), also obtained by direct methanesulphonation of the *cis*-diol.

Treatment of the *trans*-monotoluene-*p*-sulphonate (I) or the *trans*-monomethanesulphonate (VI) with cold methanolic sodium methoxide gave *cyclo*hexene oxide (III). On the other hand, similar reactions on the *cis*-toluene-*p*-sulphonate-acetate (X) and on the *cis*-methanesulphonate-acetate (XIV) gave *cyclo*hexanone (XVIII), evidently formed *via* its enol (XVII); clearly, therefore, the second general type of reaction, olefin-formation, can occur in this series when oxide-formation is not possible. There was also a very striking difference between the *cis*- and the *trans*- series in their rates of reaction with cold 0·1N-alcoholic alkali; oxide-formation from the *trans*-compounds was complete within a few minutes, whilst the production of *cyclo*hexanone from the *cis*-isomers proceeded very slowly under these conditions (see Figure). This difference in behaviour is akin to that observed by Bartlett (*J. Amer. Chem. Soc.*, 1935, **57**, 220) in the

Reaction of sulphonic esters of cyclo*hexane*-1 : 2-*diol with alkali.*



I, trans-*Monomethanesulphonate*; II, trans-*monotoluene*-p-*sulphonate*; III, cis-*monotoluene*-p-*sulphonate*.

reactions of the *cis*- and *trans*-2-chloro*cyclo*hexanols with alkali. When the *trans*-monotoluene-*p*-sulphonate (I) was heated with aqueous alkali it gave *trans-cyclo*hexane-1 : 2-diol in 58% yield, together with some formyl*cyclo*pentane; *cyclo*hexene oxide was an evident intermediate in this reaction. The *cis*-toluene-*p*-sulphonate-acetate (X) under these conditions gave *cyclo*hexanone (64%) and the *cis*-diol (22%). The formation of *cis*-diol in the latter reaction is of interest, since it indicates that the toluene-*p*-sulphonyloxy-group can be replaced by hydroxyl *without inversion*; this has already been observed in the carbohydrate field, where, for example, 3-toluene-*p*-sulphonyl di*iso*propylidene glucose can be hydrolysed, though with considerable difficulty, into di*iso*propylidene glucose (Oldham and Robertson, *J.*, 1935, 685). In the carbohydrate examples, however, there does not appear to be any evidence of the occurrence of the elimination reaction, leading to the formation of ketones.

A reaction which has assumed considerable importance in carbohydrate chemistry, but which has only recently found application in other fields (see, *e.g.*, Ruzicka, Szpilfogel, and Jeger, *Helv. Chim. Acta*, 1946, **29**, 1520), is that which occurs between a primary toluene-*p*-sulphonyl group and sodium iodide, the toluene-*p*-sulphonyloxy-residue being replaced by iodine, with quantitative precipitation of sodium toluene-*p*-sulphonate. The diagnostic value of this reaction is the basis of the so-called " Oldham–Rutherford rule " (Oldham and Rutherford, *J. Amer. Chem. Soc.*, 1932, **54**, 366) since a secondary toluene-*p*-sulphonyl group was found to be unaffected by the reagent. Some exceptions to this generalisation have been reported (Bell, Friedmann, and Williamson, *J.*, 1937, 252; Tipson and Cretcher, *J. Org. Chem.*, 1943, **8**,

95; Ness, Hann, and Hudson, *J. Amer. Chem. Soc.*, 1944, **66**, 1901), and it now appears that a secondary toluene-*p*-sulphonyl group may be reactive towards sodium iodide if it is contiguous to one in a primary position; there are also a few instances (cf. Hockett *et al.*, *ibid.*, 1946, **68**, 930) of an isolated secondary toluene-*p*-sulphonyl group reacting with sodium iodide. According to Helferich and Gnüchtel (*Ber.*, 1938, **71**, 712) a secondary methanesulphonyl group is not so resistant.

Quite recently, Tipson, Clapp, and Cretcher (*J. Org. Chem.*, 1947, **12**, 133) have shown that the toluene-*p*-sulphonates of some secondary aliphatic alcohols, and of *cyclo*hexanol, borneol, and menthol, react with sodium iodide to form sodium toluene-*p*-sulphonate; evidently the secondary toluene-*p*-sulphonyl group in these compounds is considerably more reactive than a similar group in a carbohydrate molecule, although the other products of the reaction were not identified. It has now been found that the *trans*-monotoluene-*p*-sulphonate (I) reacts readily with sodium iodide in acetone solution at 85° to give, after 5 hours, a high yield of sodium toluene-*p*-sulphonate, and from the reaction products it was possible to isolate *trans*-2-iodo-*cyclo*hexanol (XIX) as its 3 : 5-dinitrobenzoate m. p. 157°. Sodium methanesulphonate was also formed from the *trans*-monomethanesulphonate under similar conditions, though the yield of iodo*cyclo*hexanol was too low for characterisation; in both cases, unsaturated products, probably *cyclo*hexanone and *cyclo*hexadienes, were also produced. A much lower reactivity was observed with the *cis*-toluene-*p*-sulphonate-acetate (X), which required 15 hours at 100° to give 72% of sodium toluene-*p*-sulphonate; the resulting 2-iodo*cyclo*hexyl acetate (XX) was shown to be the *trans*-form by deacetylation to *trans*-2-iodo*cyclo*hexanol. A similarly low reactivity was also shown by the *cis*-methanesulphonate-acetate (XIV).

Experiments were also carried out on the replacement of toluene-*p*-sulphonyl and methane-sulphonyl groups by chlorine, and it was found that the *trans*-monotoluene-*p*-sulphonate (I) and the *trans*-monomethanesulphonate (VI) reacted smoothly with alcoholic lithium chloride to give *trans*-2-chloro*cyclo*hexanol (XXI) in *ca.* 60% yield, the tendency for substitution, rather than elimination, being predominant, unlike the situation in the reactions with sodium iodide. The *cis*-methanesulphonate-acetate (XIV) reacted less readily to give *trans*-2-chloro*cyclo*hexyl acetate (XXII), identified by methanolysis with methanolic hydrogen chloride to *trans*-2-chloro*cyclo*hexanol.

In the *cis*-compounds, the replacement of the sulphonyloxy-group is clearly accompanied by inversion; the apparent non-occurrence of inversion in the *trans*-series is undoubtedly due to the intermediate formation, by one inversion, of a cyclic compound (V) or (XXIII) (cf. Winstein *et al.*, *loc. cit.*) followed by its scission, involving a second inversion, and consequent overall retention of configuration. Winstein and Buckles, (*J. Amer. Chem. Soc.*, 1942, **64**, 2780) have observed that *cis*-2-chloro*cyclo*hexyl acetate is unaffected by silver acetate under conditions in which the *trans*-isomer readily gives *trans*-1 : 2-diacetoxy*cyclo*hexane, and have implied that the low reactivity of the *cis*-derivative is due to its inability to form an intermediate ring-compound. This view is applicable also to our own observations on the much greater reactivity of the *trans*-methanesulphonates and *trans*-toluene-*p*-sulphonates towards alkali, sodium iodide, and lithium chloride.

Experimental.

trans-cyclo*Hexane*-1 : 2-*diol*.—This was obtained by saponification of the *trans*-monoacetate, a by-product in the preparation of the monotoluene-*p*-sulphonate from *cyclo*hexene (cf. Criegee and Stanger, *loc. cit.*).

cis-cyclo*Hexane*-1 : 2-*diol*.—(i) A suspension of *cyclo*hexene (10 g.) in a solution of sodium chlorate (17 g.) in water (200 c.c.) containing osmium tetroxide (0·1 g.) was vigorously stirred for 9 hours at 50°. The cooled solution was then extracted twice with benzene to remove catalyst, and then evaporated to dryness. Extraction of the residue with boiling chloroform gave the *cis*-diol (6·5 g.), m. p. 98° after one recrystallisation from carbon tetrachloride. This method was used by Böeseken and Giffen (*Rec. Trav. chim.*, 1920, **39**, 183), but no yield was recorded.

(ii) A solution of potassium permanganate (40 g.) and magnesium sulphate (30 g., anhydrous) in water (800 c.c.) was added gradually to a vigorously stirred suspension of *cyclo*hexene (26 g.) in ethanol (600 c.c.) during 1·5 hours, the temperature being kept between −15° and −20°. After filtration, the solution was concentrated to small bulk, saturated with salt, and extracted with chloroform to yield the *cis*-diol (12 g., 33%), m. p. 98°. Markownikoff (*Annalen*, 1898, **302**, 21) obtained a yield of 18%.

Derivatives of trans-cyclo*Hexane*-1 : 2-*diol*.—Treatment of the diol with slight excess of methane-sulphonyl chloride in pyridine solution for 12 hours at ordinary temperature gave the trans-*dimethane-sulphonate*, which crystallised from methanol in needles, m. p. 135° (Found: C, 35·9; H, 6·0. $C_8H_{16}O_6S_2$ requires C, 35·3; H, 5·9%). Similar treatment of the *trans*-monotoluene-*p*-sulphonate, prepared by the method of Criegee and Stanger (*loc. cit.*), gave the trans-*toluene*-p-*sulphonate-methanesulphonate*, which crystallised from methanol in rosettes of needles, m. p. 108·5° (Found: C, 48·7; H, 6·0. $C_{14}H_{20}O_6S_2$ requires C, 48·3; H, 5·8%).

To a solution of *cyclo*hexene oxide (1·75 g.) in dry ether (25 c.c.) a solution of methanesulphonic acid

(1·75 g.) in ether (10 c.c.) was gradually added, with cooling. After an hour at 20°, removal of the solvent gave a quantitative yield of the trans-*monomethanesulphonate*, which crystallised from light petroleum (b. p. 80—100°) in fine needles, m. p. 79° (Found: C, 43·3; H, 7·4. $C_7H_{14}O_4S$ requires C, 43·3; H, 7·3%). With toluene-*p*-sulphonyl chloride in pyridine solution, this readily gave the *trans*-toluene-*p*-sulphonate-methanesulphonate, m. p. 108·5°, identical with that described above. The same monomethanesulphonate was also isolated, in 12% yield, by fractional crystallisation from carbon tetrachloride of the mixture of products obtained by treatment of the *trans*-diol in pyridine solution with one mol. of methanesulphonyl chloride.

Derivatives of cis-cyclo*Hexane*-1 : 2-*diol*.—With a slight excess of methanesulphonyl chloride in pyridine solution, the cis-*bismethanesulphonate* was obtained, which crystallised from methanol in rosettes of needles, m. p. 85·5° (Found: C, 35·5; H, 6·0. $C_8H_{16}O_6S_2$ requires C, 35·3; H, 5·9%).

The *trans*-toluene-*p*-sulphonate-acetate, isolated as a by-product in the preparation of the *trans*-monotoluene-*p*-sulphonate (cf. Criegee and Stanger, *loc. cit.*) was converted by treatment in alcoholic solution with calcium carbonate into the *cis*-monoacetate, according to the method of Winstein and Buckles (*loc. cit.*). The product was isolated by concentration of the filtered solution, dilution with water, and extraction with ether; it had b. p. 110—113°/11 mm., $n_D^{29°}$ 1·4623. This monoacetate (11·2 g.) dissolved in pyridine (60 c.c.) was treated with toluene-*p*-sulphonyl chloride (15 g.) and left overnight. Chloroform (250 c.c.) was then added, and the solution was washed with dilute sulphuric acid and finally with water. After drying, removal of solvent gave the cis-*toluene*-p-*sulphonate-acetate*, which crystallised from methanol in prisms, m. p. 80°, depressed to *ca.* 60° on admixture with the *trans*-isomer mentioned above (Found: C, 57·6; H, 6·3. $C_{15}H_{20}O_5S$ requires C, 57·65; H, 6·5%). Similar treatment of the *cis*-monoacetate (8 g.) in pyridine (30 c.c.) with methanesulphonyl chloride (6·4 g.) gave the cis-*methanesulphonate-acetate*, which crystallised from methanol in large prisms, m. p. 64° (Found: C, 45·7; H, 6·9. $C_9H_{16}O_5S$ requires C, 45·7; H, 6·8%).

The *cis*-toluene-*p*-sulphonate-acetate (1·1 g.) was dissolved in 0·2% methanolic hydrogen chloride (20 c.c.) and left at 20° overnight. After neutralisation with sodium hydrogen carbonate and removal of solvent, the residue was taken up in chloroform, dried (Na_2SO_4), and then evaporated to give the cis-*monotoluene*-p-*sulphonate* as a viscous oil (yield, almost theoretical) (Found: S, 11·8. $C_{13}H_{18}O_3S$ requires S, 11·8%). A portion, with toluene-*p*-sulphonyl chloride in pyridine, furnished the *cis*-bistoluene-*p*-sulphonate m. p. 129°, whilst with methanesulphonyl chloride in pyridine it gave the cis-*toluene*-p-*sulphonate-methanesulphonate*, prisms from aqueous ethanol, m. p. 75° (Found: C, 48·25; H, 5·9. $C_{14}H_{20}O_6S_2$ requires C, 48·3; H, 5·8%).

Deacetylation of the *cis*-methanesulphonate-acetate under similar conditions gave the cis-*monomethanesulphonate* as a water-soluble viscous oil, b. p. *ca.* 80°/0·0001 mm. (Found: S, 16·5. $C_7H_{14}O_4S$ requires S, 16·5%). A portion, treated in pyridine solution with methanesulphonyl chloride, gave the *cis*-bismethanesulphonate, m. p. and mixed m. p. 85·5°.

Reactions of the Monotoluene-p-*sulphonates and Monomethanesulphonates with Alkali*.—(i) The *trans*-monotoluene-*p*-sulphonate (19·7 g.) in methanol (60 c.c.) was treated with methanolic sodium methoxide (34 c.c.; 2·17 N) at room temperature overnight; sodium toluene-*p*-sulphonate had then separated from the solution, which was still alkaline to phenolphthalein. After neutralisation with carbon dioxide, and filtration, the methanol was removed by distillation through a 6-inch Vigreux column; it nevertheless had a strong odour of *cyclo*hexene oxide. The liquid residue was diluted with ether (100 c.c.), washed with water, and dried (Na_2SO_4). After removal of ether through the Vigreux column, the residual *cyclo*hexene oxide distilled at 130—132°, $n_D^{20°}$ 1·4491 (yield 1·6 g.). It was characterised by reaction with methanesulphonic acid, under the conditions already described, to give the *trans*-monomethanesulphonate, m. p. 79°.

(ii) The *trans*-monomethanesulphonyl derivative (18 g.), on similar treatment, gave 1·5 g. of *cyclo*hexene oxide, b. p. 129—131°, $n_D^{21°}$ 1·4492.

(iii) The *cis*-toluene-*p*-sulphonate-acetate (19 g.) on treatment in methanol solution with methanolic sodium methoxide (28·4 c.c., 2·17N) at room temperature overnight gave *cyclo*hexanone, 2·9 g., b. p. 155°, characterised as the semicarbazone, m. p. 165·5°, and the 2 : 4-dinitrophenylhydrazone, m. p. 161°. It is noteworthy that only one equivalent of methoxide was required; the acetyl group is removed as methyl acetate by catalytic alcoholysis.

(iv) The *cis*-methanesulphonate-acetate (7 g.) similarly yielded *cyclo*hexanone, 1·3 g., b. p. 150—160°.

(v) The *trans*-monotoluene-*p*-sulphonate (16 g.) in 0·5N-aqueous sodium hydroxide (119 c.c.) was stirred at 85—90° for 2·5 hours. A strong odour of *cyclo*hexene oxide was observed during the first ½ hour. The clear neutral solution was extracted once with chloroform (20 c.c.) to yield a trace of an oil which gave a positive Schiff test for aldehyde, and gave *formyl*cyclo*pentane* 2 : 4-*dinitrophenylhydrazone*, orange plates from methanol, m. p. 158° (Found: N, 19·9. $C_{12}H_{14}O_4N_4$ requires N, 20·1%). The aqueous solution, on evaporation to dryness and extraction of the solid residue with chloroform, gave *trans-cyclo*hexane-1 : 2-diol (3·94 g.; 58%), m. p. 100°, raised to 104° on recrystallisation.

(vi) The *cis*-toluene-*p*-sulphonate-acetate (9·0 g.) in 0·5N-sodium hydroxide (115 c.c.) was stirred at 85—90° for 7 hours. The cooled solution was then saturated with salt and extracted with ether to yield *cyclo*hexanone (1·8 g.; 63·7%), b. p. 155° (semicarbazone, m. p. 165°). Evaporation of the aqueous portion to dryness, followed by extraction with chloroform, gave *cis-cyclo*hexane-1 : 2-diol (0·75 g.; 22·4%), m. p. 92°, raised to 94° on admixture with an authentic sample of m. p. 98°. It was characterised by conversion into the *cis*-bismethanesulphonate, m. p. and mixed m. p. 85°.

(vii) Quantitative experiments on the rates of reaction with alkali of the *trans*-monomethanesulphonate, *trans*-monotoluene-*p*-sulphonate, and *cis*-monotoluene-*p*-sulphonate were carried out according to the following procedure. The compound (0·025 mol.) was dissolved in methanol (25 c.c.) and treated with methanolic potassium hydroxide (25 c.c., 0·2N; 100% excess). The solution was kept at 17°, the progress of the reaction, measured by the consumption of alkali, being followed by withdrawal of 10 c.c. portions and titration with standard acid. The results are shown in the figure.

Reactions with Sodium Iodide.—(i) The *trans*-monotoluene-*p*-sulphonate (5 g.) and sodium iodide (8 g.) in acetone (50 c.c.) were heated in a sealed tube at 85° for 5 hours. Sodium toluene-*p*-sulphonate

(2·9 g., 81%) was removed by filtration, and the acetone distilled off through a Vigreux column; the distillate was unsaturated towards bromine in carbon tetrachloride. The residue, which contained free iodine, was diluted with water (20 c.c.) and extracted with four 40-c.c. portions of ether. The extracts were washed with aqueous sodium thiosulphate until colourless, then dried (Na_2SO_4) and evaporated to an oil (1·75 g.). Distillation at 50—60° (bath temp.)/0·001 mm. gave a pale yellow oil (0·65 g.), the residue consisting of unchanged monotoluene-*p*-sulphonate. The distillate (Found: I, 30·8%) contained 2-iodo*cyclo*hexanol, which could not be isolated in the pure state, but was identified by formation of its 3 : 5-dinitrobenzoate, crystallising from ethanol in needles, m. p. 157° (Found: I, 30·2. Calc. for $C_{13}H_{13}O_6N_2I$: I, 30·2%). Tiffeneau and Tchoubar (*Compt. rend.*, 1938, **207**, 918) give m. p. 157° for this derivative of *trans*-2-iodo*cyclo*hexanol.

(ii) Under the same conditions, the *trans*-monomethanesulphonate (5 g.) gave 2·2 g. of sodium methanesulphonate (74%), but the small amount of iodine-containing oil, which was obtained on distillation, could not be effectively separated from unchanged monomethanesulphonate.

(iii) Under the same conditions, the *cis*-toluene-*p*-sulphonate-acetate gave only 6·5% of sodium toluene-*p*-sulphonate, but when this compound (1·5 g.) was heated with sodium iodide (2·2 g.) in acetone (15 c.c.) at 100° for 15 hours, the sodium toluene-*p*-sulphonate collected from the cooled solution amounted to 0·67 g. (72%). The product was worked up to give an oil (0·5 g.) which on distillation at 80° (bath temp.)/0·0001 mm. gave a sulphur-free oil (0·17 g.) and a residue (0·3 g.) of unchanged toluene-*p*-sulphonate-acetate. The 2-iodo*cyclo*hexyl acetate (0·15 g.) was deacetylated by being kept overnight in 0·2% methanolic hydrogen chloride (1 c.c.). Removal of solvent than gave an oil (0·1 g.) which was treated with 3 : 5-dinitrobenzoyl chloride (0·12 g.) in pyridine (1 c.c.). The solid derivative contained some methyl 3 : 5-dinitrobenzoate, evidently formed from a trace of residual methanol, but by several fractional crystallisations from methanol, the less soluble material being discarded on each occasion, a small quantity of *trans*-2-iodo*cyclo*hexyl 3 : 5-dinitrobenzoate was obtained. It had m. p. 153°, and was insufficient for a further recrystallisation, but the m. p. was raised to 156° on admixture with an authentic sample of m. p. 157°. Brunel (*Ann. Chim. Phys.*, 1905, **6**, 217) described a 2-iodo*cyclo*hexyl acetate to which he allocated a *cis*-configuration, but in the light of more recent evidence this was almost certainly the *trans*-compound, and therefore identical with that obtained above.

(iv) The *cis*-methanesulphonate-acetate (1·65 g.) on being heated with sodium iodide (3·15 g.) in acetone (20 c.c.) at 100° for 16 hours gave 0·7 g. (85%) of sodium methanesulphonate. The product distilled at 80° (bath temp.)/0·0002 mm., as an oil (0·58 g.) containing iodine and sulphur, and was evidently contaminated with unchanged methanesulphonate. It was deacetylated with methanolic hydrogen chloride as above, but the presence of methanesulphonate prevented the isolation of any crystalline derivatives of the iodo-compound.

Reactions with Lithium Chloride.—(i) A solution of the *trans*-monotoluene-*p*-sulphonate (5 g.) and lithium chloride (2·4 g.) in ethanol (100 c.c.) was refluxed for 30 hours, and then concentrated to small volume, diluted with water (25 c.c.), and extracted thrice with 30-c.c. portions of chloroform. The extracts, after being dried (Na_2SO_4), were evaporated to an oil, which on distillation furnished *trans*-2-chloro*cyclo*hexanol (1·6 g.; 64%), b. p. 81—85°/14 mm., $n_D^{20°}$ 1·4850, characterised as the α-naphthylurethane, m. p. 165°. Bartlett (*loc. cit.*) recorded m. p. 165°.

(ii) Similar treatment of the *trans*-monomethanesulphonate (2 g.) gave 0·8 g. (57·5%) of *trans*-2-chloro*cyclo*hexanol (α-naphthylurethane, m. p. 165°).

(iii) The *cis*-methanesulphonate-acetate (4 g.), under the same conditions, gave only 0·6 g. (20%) of 2-chloro*cyclo*hexyl acetate, b. p. 105—110°/25 mm., which was deacetylated by treatment with 0·2% methanolic hydrogen chloride at room temperature for 15 hours. The resulting 2-chloro*cyclo*hexanol was identified as the *trans*-form by conversion into the α-naphthylurethane, m. p. and mixed m. p. 165°.

Thanks are due to the Department of Scientific and Industrial Research for a maintenance allowance to one of us (M. F. C.).

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[*Received, April 5th*, 1948.]

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75. *Alicyclic Glycols. Part II. Derivatives of* cyclo*Hexane*-1 : 4-*diol.*

By L. N. OWEN and P. A. ROBINS.

A study has been made of the properties of the *mono-* and *di-toluene*-p-*sulphonyl* derivatives of *cis-* and *trans-cyclo*hexane-1 : 4-diol. With alcoholic alkali, no 1 : 4-epoxide is formed, the main reaction being intramolecular elimination of toluene-*p*-sulphonic acid, with formation of *cyclo*hexenol or *cyclo*hexadienes. With potassium acetate, lithium chloride, and sodium iodide, the toluene-*p*-sulphonyloxy-groups are replaced by acetoxy-, chlorine, and iodine, respectively, though the simultaneous formation of olefinic products is usually observed. Improved methods are described for the preparation of the mono-acetates and -benzoates of the diol. With thionyl chloride, the *trans*-diol gives a polymeric sulphite ester.

IN Part I (preceding paper), an account has been given of some reactions of the mono-methanesulphonyl and -toluene-*p*-sulphonyl derivatives of *cyclo*hexane-1 : 2-diol, and it has been shown that the 1 : 2-epoxide is formed only when the sulphonyl group is *trans* in relation to the adjacent hydroxyl. In the carbohydrate field, it has been recognised for some time that when no actual

or potential hydroxyl group is available in the *trans*-position on the adjacent carbon atom, it may be possible for an oxide ring of a different type to be formed. It is in such circumstances that compounds such as the 3 : 6-anhydro-sugars can be prepared, in which the anhydro-ring is very much more stable than one of the ethylene oxide type (see Peat, " Advances in Carbohydrate Chemistry ", Vol. II, p. 56).

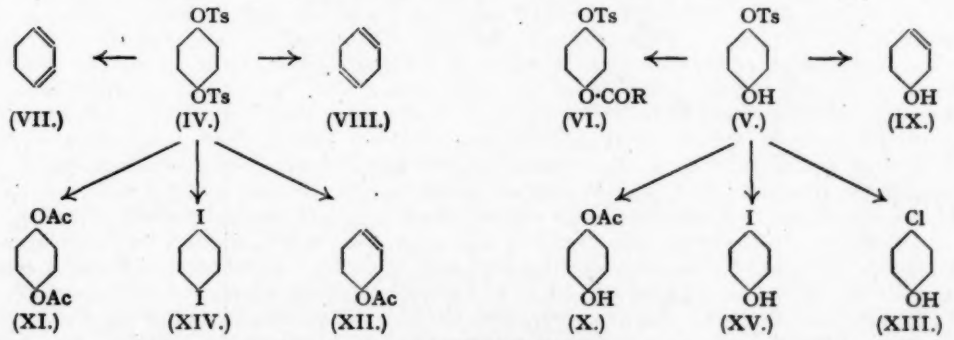
1 : 4-Cineole (I) provides a comparable example of a five-membered ring oxide in the alicyclic field, but it is only recently that the parent compound, 1 : 4-epoxy*cyclo*hexane (II) has been described. This has been obtained by Olberg, Pines, and Ipatieff (*J. Amer. Chem. Soc.*, 1944,

(I.) (II.) (II*a*.) (III.)

66, 1096) by direct dehydration of *cyclo*hexane-1 : 4-diol over alumina, and also by Nudenberg and Butz (*ibid.*, p. 307) by hydrogenation of 1 : 4-epoxy*cyclo*hex-2-ene (III), prepared by condensation of furan with ethylene. Stereochemical considerations require a *cis* disposition of the oxide ring, probably in conjunction with a stabilised boat form for the *cyclo*hexane ring (II*a*), and, according to Ipatieff and Pines, the yield of oxide (73%) from the *trans*-diol is much higher than that from the *cis*-, which supports the suggestion of inversion during the reaction. With hydrogen bromide, the oxide gives *trans*-1 : 4-dibromo*cyclo*hexane (Ipatieff and Pines, *loc. cit.*), and, with acetic anhydride, the diacetate of *trans-cyclo*hexane-1 : 4-diol (Nudenberg and Butz, *loc. cit.*). The former reaction presumably proceeds in two stages, *via* 4-bromo*cyclo*hexanol, and it is possible that inversion occurs in the final replacement of hydroxyl by bromine. The reaction with acetic anhydride, also, may be a two-stage process if the anhydride contains traces of acetic acid, but acetylation of the intermediate 4-acetoxy*cyclo*hexanol would not be expected to cause inversion, so that this must occur at the ring-opening stage.

It occurred to us that it might be possible to prepare the epoxide from a *trans*-monotosyl derivative of the diol, and although this aim was not realised, the properties of the toluene-*p*-sulphonyl derivatives themselves proved to be of some interest.

*cyclo*Hexane-1 : 4-diol was prepared by hydrogenation of quinol in methanol at 150° and 120 atm., with a Raney nickel catalyst, care being taken to ensure complete reduction, since traces of unchanged quinol cause considerable difficulty in the subsequent separation of stereoisomers. The diol was converted into the diacetate, from which the *trans*-form, m. p. 102—103°, was isolated by crystallisation, first from acetone, and finally from methanol; the residual *cis*-diacetate was then purified by distillation. Previous workers (cf. Ipatieff and Pines, *loc. cit.*) have used the ordinary saponification procedure for regeneration of the diols from the diacetates, but this has now been considerably simplified by adoption of the catalytic method of alcoholysis devised and used by Zemplén (*Ber.*, 1923, **56**, 1705; 1929, **62**, 1613; 1936, **69**, 1827) in the carbohydrate field. The stereochemically pure diacetates, dissolved or suspended in dry methanol, were separately treated with a trace of sodium methoxide and left for a few hours at room temperature; removal of solvent then yielded the diols in substantially pure stereochemical



(Ts = *p*-$CH_3 \cdot C_6H_4 \cdot SO_2$)

forms. These reacted readily with two mols. of toluene-*p*-sulphonyl chloride in pyridine to give the corresponding *bistoluene*-p-*sulphonyl* derivatives (IV), *cis*-, m. p. 98—99°, *trans*-, m. p. 157°.

By reaction with one mol. of toluene-*p*-sulphonyl chloride in chloroform solution, added to the diols in pyridine at 0°, good yields of the *monotoluene*-p-*sulphonyl* derivatives (V), *cis*-, m. p. 94°; *trans*-, m. p. 112°; were obtained. Benzoylation of the latter compounds gave the *benzoyltoluene*-p-*sulphonyl* derivatives (VI; R = Ph), in which the usual order of m. p. was reversed, *cis*-, m. p. 152°; *trans*-, m. p. 94—95°; the same anomaly occurred with the *toluene*-p-*sulphonylacetyl*-derivatives (VI; R = Me), *cis*-, m. p. 104°; *trans*-, m. p. 81—83°. Several similar examples have been encountered in the present work, thus again emphasising the unreliability of relative m. p. as a criterion of configuration.

Reaction of the bistoluene-*p*-sulphonyl derivatives (IV) with alcoholic alkali, or with alcoholic alkoxides, resulted in the removal of two mols. of toluene-*p*-sulphonic acid, and formation of a mixture of *cyclo*hexa-1 : 3- (VII) and -1 : 4-(VIII)-dienes, the presence of the former being confirmed by its absorption spectrum. Probably because of the high volatility of these dienes, the yield in no case exceeded 25%, but there was no evidence of any epoxide formation in these reactions. The monotoluene-*p*-sulphonyl derivatives (V), on reaction with either aqueous alkali, alcoholic alkali, or acid, gave only *cyclo*hexen-4-ol (IX), and this product was also formed by heating with methanol alone in a sealed tube at 100°. It is therefore clear that, under the conditions employed, the toluene-*p*-sulphonyl derivatives of *cyclo*hexane-1 : 4-diol give the corresponding unsaturated compounds, rather than ethers, thus behaving like the *cis*-monotoluene-*p*-sulphonyl derivative of the 1 : 2-diol (see Part I).

Investigations were then carried out on the replacement of the toluene-*p*-sulphonyl groups in these compounds by acetyl or halogen. Reaction of the *trans*-monotoluene-*p*-sulphonate with potassium acetate in boiling ethanol proceeded largely with loss of toluene-*p*-sulphonic acid, titration showing its formation to the extent of 85%; consequently, the main product isolated was *cyclo*hexen-4-ol, but, in addition, there was obtained in small yield a monoacetate of the diol, which gave a 3 : 5-*dinitrobenzoate*, m. p. 153—154°. For the 3 : 5-dinitrobenzoates of the *cis*- and *trans*-monoacetates of *cyclo*hexane-1 : 4-diol, Dimroth (*Ber.*, 1939, **72**, 2043) gives m. p. 119—122° and 145—146° respectively. Dimroth's " *cis* "-derivative, however, was prepared from the residues after crystallisation of *trans*-monoacetate, and was evidently not stereochemically pure, since we have now obtained the *cis*-3 : 5-dinitrobenzoate-acetate from pure *cis*-diol (see below) and find it to melt at 154—155°, and to be identical with the derivative mentioned above. The *trans*-monotoluene-*p*-sulphonate therefore gives a small amount of *cis*-monoacetate (X). The *trans*-bistoluene-*p*-sulphonate, under similar conditions, gave a high yield of toluene-*p*-sulphonic acid and volatile *cyclo*hexadienes, but again it was possible to show that replacement, with inversion, had also occurred, since both the *trans*-diacetate (XI) and the acetate (XII) of *cyclo*hexen-4-ol were identified. Evidently, however, the tendency for the formation of olefinic compounds is again the predominating factor.

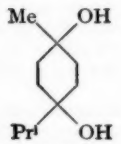
One experiment was carried out on the replacement of toluene-*p*-sulphonyloxy by chlorine, in which the *cis*-monotoluene-*p*-sulphonate (V), treated with lithium chloride in boiling ethanol, gave 4-chloro*cyclo*hexanol (XIII). This was shown, by fractional crystallisation of the phenylurethanes, to be a mixture of *cis*- and *trans*-forms, with the latter predominating, thus indicating that the replacement had occurred with a high proportion of inversion; the development of acidity in the reaction mixture indirectly indicated the formation also of some *cyclo*hexen-4-ol.

On treatment of the *cis*-bistoluene-*p*-sulphonate with sodium iodide in boiling acetone solution, sodium toluene-*p*-sulphonate was precipitated in almost theoretical yield, and a mixture of *cis*- and (mainly) *trans*-di-iodo*cyclo*hexanes (XIV) was isolated; from the *trans*-bistoluene-*p*-sulphonates only the *trans*-di-iodide could be obtained. This suggests partial inversion in the former reaction and probably complete inversion in the latter (since inversion at both the 1 and 4 positions results in retention of the original configuration), but the yields of di-iodides were low in both reactions, and it is likely that *cyclo*hexadienes were formed simultaneously. The *trans*-monotoluene-*p*-sulphonate (V) yielded mainly 4-*iodo*cyclo*hexanol* (XV), the configuration of which could not be established because of its failure to give any crystalline derivatives.

In addition to the attempts, described above, to prepare 1 : 4-epoxy*cyclo*hexane from the toluene-*p*-sulphonyl derivatives, investigations were carried out to determine whether the oxide was formed under conditions in which 1 : 4-terpin (XVI) is known to be converted into 1 : 4-cineole (cf. Wallach, *Annalen*, 1907, **356**, 204), but steam distillation of the diol in either oxalic or sulphuric acids gave *cyclo*hexen-4-ol as the only identifiable product. One further attack on the problem was made by dehydrochlorination experiments on 4-chloro*cyclo*hexanol, prepared in improved yield (*ca.* 60%) from the diol by the action of fuming hydrochloric acid at 80—90° (cf. Palfray *et al.*, *Bull. Soc. chim.*, 1928, **43**, 906; *Compt. rend.*, 1929, **189**, 701). The

chlorohydrin failed to react with potassium hydroxide in boiling ether; with refluxing alcoholic alkali, or solid potassium hydroxide at 160°, a complex mixture was obtained. At present, therefore, the process of Ipatieff and Pines is still the only method for the preparation of 1 : 4-epoxy*cyclo*hexane from the 1 : 4-diol.

In attempts to prepare 4-chloro*cyclo*hexanol by reaction of the *trans*-diol with one mol. of thionyl chloride under various conditions, there was obtained, in good yield, a pale brown amorphous solid, soluble in chloroform, from which it was precipitated by gradual addition of ether or light petroleum. Fractionation in this way gave a series of buff-coloured solids of decreasing m. p., all of which contained sulphur, but no halogen, and gave, on saponification with alcoholic potassium hydroxide, potassium sulphite and the original *trans*-diol. The material is therefore formulated as a polymeric sulphite ester (XVII).



(XVI.)

(XVII.)

(XVIII.)

The few reports in the literature indicate considerable difficulty in obtaining mono-esters of cyclohexane-1 : 4-diol, either by partial esterification of the diol, or by partial saponification of the di-esters (Rothstein *et al.*, *Compt. rend.*, 1928, **186**, 1007; *Bull. Soc. chim.*, 1929, **45**, 855; *Ann. Chim.*, 1930, **14**, 461). Dimroth (*loc. cit.*) claimed the isolation, in poor yield, of both the *cis*- and *trans*-monoacetates by partial saponification of the mixed diacetates under rigorously controlled conditions. A crystalline monobenzoate of the *trans*-diol was also reported to be formed, in low yield, by the Schotten–Baumann process. These mono-esters are important in that they provide, on oxidation, esters of 4-hydroxy*cyclo*hexanone, a compound of potential value for the synthesis of hydroxypolycyclic compounds (cf. Aldersley and Burckhardt, *J.*, 1938, 545; Dimroth, *loc. cit.*), and improved methods for their preparation are desirable. In view of the ready formation, in good yield, of the monotoluene-*p*-sulphonates by the method already described, it was thought that other mono-esters could be obtained by similar means. By addition of one mol. of the appropriate acid chloride, in chloroform solution, to a pyridine solution of the stereochemically pure diol at 0°, the following yields were obtained: *trans*-monobenzoate, 78%; *cis*-monobenzoate, 48%; *trans*-monoacetate, 45%; *cis*-monoacetate, 47%. The monoacetates were characterised by conversion into their 3 : 5-dinitrobenoates, *cis*-, m. p. 154—155° (see above), and *trans*-, m. p. 146—147°. Furthermore, toluene-*p*-sulphonation of the *cis*-monoacetate and *cis*-monobenzoate gave the toluene-*p*-sulphonyl acetate and the toluene-*p*-sulphonyl benzoate, identical with those already prepared by acetylation or benzoylation of the *cis*-monotosylate. Both the *cis*- and *trans*-monobenzoates were oxidised by chromic acid to 4-benzoyloxy*cyclo*hexanone (XVIII) (*semicarbazone*); since completion of this work, a more recent publication of Dimroth has become available (*Ber.*, 1942, **75**, 317) in which the preparation of this ester of 4-hydroxy*cyclo*hexanone is described, though in much lower overall yield.

Experimental.

(Light petroleum, unless stated otherwise, refers to the fraction, b. p. 40—60°.)

cis- *and* trans-cyclo*Hexane*-1 : 4-*diol*.—Quinol (200 g.) in methanol (200 c.c.) was hydrogenated at 150° and 150 atm. over Raney nickel (20 g.) until no more hydrogen was absorbed (*ca.* 20 hours). The product, isolated by evaporation of the filtered solution, was acetylated by refluxing for 4 hours with acetic anhydride (400 g.), and the crude diacetate crystallised from boiling acetone (200 c.c.) to give long prisms of the *trans*-compound, m. p. 102—103° after two recrystallisations from methanol (yield, 130 g.). The oil recovered from the acetone mother liquors was diluted with benzene (50 c.c.), treated with light petroleum (100 c.c.), and seeded with *trans*-diacetate, to give a further 13 g. of this material. The residual solution was evaporated and distilled to give the *cis*-diacetate (130 g.), m. p. 35°, b. p. 130°/15 mm.

The *trans*-diacetate (130 g.) was covered with anhydrous methanol (200 c.c.) and treated with 20% methanolic sodium methoxide (2·5 c.c.). After 24 hours' standing with occasional shaking, the solid had dissolved, and the solution, concentrated to 90 c.c., was treated with ether (400 c.c.) and cooled to 0°, to give small prisms of the *trans*-diol (72 g.), m. p. 141°. The *cis*-diacetate (130 g.) was similarly treated, the crude product obtained by evaporation of the reaction mixture being crystallised from boiling acetone. The *cis*-diol was obtained as large prisms (25 g.), m. p. 108—110°; further quantities of less pure material were obtained from the mother liquors. It is particularly important that the diacetates be free from traces of quinol diacetate, since this inhibits the catalytic deacetylation, probably owing to reaction of the sodium methoxide with quinol.

Toluene-p-*sulphonyl Derivatives.*—(*a*) The *trans*-diol (20 g.), dissolved in dry pyridine (100 c.c.), was treated with toluene-*p*-sulphonyl chloride (68 g.), left overnight, and then poured into excess of dilute hydrochloric acid. The precipitated solid was collected, washed with water, dried, and crystallised from benzene to give the trans-*bistoluene*-p-*sulphonate* (61 g.) as needles, m. p. 159° (decomp., after rapid heating from 150°) (Found: C, 56·9; H, 5·75. $C_{20}H_{24}O_6S_2$ requires C, 56·6; H, 5·7%).

(*b*) The *cis*-diol (5 g.) similarly gave needles of the cis-*bistoluene*-p-*sulphonate* (13·3 g.), m. p. 98—99° after crystallisation from methanol (Found: C, 56·3; H, 5·5%).

(*c*) The *trans*-diol (20 g.) in pyridine (100 c.c.) was cooled to 0° and treated with a solution of toluene-*p*-sulphonyl chloride (32 g.) in pure chloroform (100 c.c.), added with stirring during 2 hours. After standing overnight, the trans-*monotoluene*-p-*sulphonate* (37 g.) was isolated; it crystallised from benzene–light petroleum (b. p. 60—80°) in needles, m. p. 111° (Found: C, 57·6; H, 6·3. $C_{13}H_{18}O_4S$ requires C, 57·75; H, 6·7%). With benzoyl chloride in pyridine it gave the trans-*benzoate-toluene*-p-*sulphonate*, plates from aqueous ethanol, m. p. 94—95° (Found: C, 64·2; H, 5·8. $C_{20}H_{22}O_5S$ requires C, 64·15; H, 5·9%). Acetylation gave the trans-*toluene*-p-*sulphonate-acetate*, long needles from benzene–light petroleum, m. p. 81—83° (Found: C, 57·6; H, 6·4. $C_{15}H_{20}O_5S$ requires C, 57·7; H, 6·45%).

(*d*) The cis-*monotoluene*-p-*sulphonate*, prepared in a similar way, crystallised from benzene–light petroleum (b. p. 60—80°) in needles, m. p. 94—95° (Found: C, 57·7; H, 6·7%). Benzoylation gave the cis-*benzoate-toluene*-p-*sulphonate*, prisms from ethanol, m. p. 150—151° (Found: C, 63·9; H, 5·9%). The cis-*toluene*-p-*sulphonate-acetate* crystallised from benzene–light petroleum in prisms, m. p. 104—105° (Found: C, 57·6; H, 6·55%).

Action of Alkali on the Toluene-p-*sulphonyl Derivatives.*—(*a*) The *trans*-bistoluene-*p*-sulphonate (15 g.) was heated with 5% ethanolic potassium hydroxide (150 c.c.) for 2 hours under partial reflux, 10 c.c. of distillate being collected in an ice-cooled receiver. The absorption spectrum of a portion of this distillate indicated the presence of *ca.* 2% of the conjugated *cyclo*hexa-1 : 3-diene. The distillate was diluted with several volumes of light petroleum, washed with water to remove alcohol, and treated with excess of bromine; on evaporation, a mixture of tetrabromo*cyclo*hexanes (2·5 g.), m. p. *ca.* 120°, was obtained, corresponding to a 20% yield of *cyclo*hexadienes. The main reaction mixture was neutralised with carbon dioxide, filtered, and concentrated to small bulk under a 12-inch Dufton column. The residue was diluted with water and extracted with ether. Removal of ether from the dried extracts gave only 0·5 g. of liquid residue, b. p. 64—66°/44 mm., $n_D^{21°}$ 1·4510, which was not 1 : 4-epoxy*cyclo*hexane; it was possibly the diethyl ether of the diol, but there was not enough for identification.

Essentially similar results were obtained with the *cis*-bistoluene-*p*-sulphonate, and also by the use of sodium methoxide or *tert.*-butoxide in place of the alkali.

(*b*) The *trans*-monotoluene-*p*-sulphonate (10 g.) in 5% aqueous potassium hydroxide (100 c.c.) was heated to 110°, with vigorous stirring, the distillate (containing oily drops) being collected. Water was added to the mixture at a rate sufficient to maintain its volume during the heating. When 100 c.c. had been collected, the distillate was saturated with salt and extracted with ether. The extracts were dried (Na_2SO_4), and the ether removed through a Dufton column. The residual oil (2·4 g.), b. p. 68—69°/16 mm., $n_D^{17°}$ 1·4820, was identified as *cyclo*hexen-4-ol by formation of the α-naphthylurethane, m. p. 132—133° (lit. 128°) (Found: C, 76·65; H, 6·45. Calc. for $C_{17}H_{17}O_2N$: C, 76·4; H, 6·4%).

Similar treatment of the *trans*-monotoluene-*p*-sulphonate with 5% methanolic potassium hydroxide again gave *cyclo*hexen-4-ol. Furthermore, the same product was obtained when a solution of the monotoluene-*p*-sulphonate (2 g.) in methanol (20 c.c.) was heated at 100° for 15 hours. There was no indication of the formation of 1 : 4-epoxy*cyclo*hexane in any of the above experiments.

Acid Hydrolysis of the trans-*Monotoluene*-p-*sulphonate.*—The compound (5 g.) in methanol (20 c.c.) and 2N-aqueous hydrochloric acid (20 c.c.) was heated under reflux for an hour, cooled, neutralised with sodium hydrogen carbonate, and concentrated under a Dufton column. The aqueous residue, saturated with salt, was thoroughly extracted with ether. Removal of solvent from the dried extracts gave *cyclo*hexen-4-ol (0·7 g.), b. p. 67—69°/15 mm., characterised as the α-naphthylurethane, m. p. 132—133°.

Reaction of the trans-*Monotoluene*-p-*sulphonate with Potassium Acetate.*—The derivative (10 g.) and potassium acetate (10 g.) in ethanol (100 c.c.) were refluxed for 15 hours. The mixture then required 31·4 c.c. of N-sodium hydroxide for neutralisation to phenolphthalein, representing an 85% yield of acetic acid. It was saturated with salt, and extracted with ether. The dried (K_2CO_3) extracts were evaporated to an oil, which on distillation gave *cyclo*hexen-4-ol (0·9 g.); 3 : 5-*dinitrobenzoate*, m. p. 101—102° (Found: C, 53·35; H, 4·1. $C_{13}H_{12}O_6N_2$ requires C, 53·4; H, 4·15%). The residue from the distillation was dissolved in pyridine (5 c.c.) and treated with 3 : 5-dinitrobenzoyl chloride, to give cis-cyclo*hexane*-1 : 4-*diol* 3 : 5-*dinitrobenzoate-acetate*, which crystallised from ethanol in needles (0·1 g.), m. p. 153—154° (Found: C, 51·5; H, 4·85. $C_{15}H_{16}O_8N_2$ requires C, 51·15; H, 4·6%).

Reaction of the trans-*Bistoluene*-p-*sulphonate with Potassium Acetate.*—The bistoluene-*p*-sulphonate (5 g.) and potassium acetate (5 g.) in ethanol (100 c.c.) were refluxed for 22 hours. On cooling, potassium toluene-*p*-sulphonate (4·4 g.) separated, and was removed. The filtrate was concentrated, diluted with water, and extracted with chloroform. Removal of solvent from the dried (Na_2SO_4) extracts gave an oil (0·7 g.) which slowly deposited a small quantity of *trans*-diacetate, m. p. and mixed m. p. 101°. The residual oil gave a blue colour with alcoholic sulphuric acid, suggesting the presence of *cyclo*hexenyl acetate (Lindemann and Baumann, *Annalen*, 1930, **477**, 48), and it was therefore dissolved in ethanol, treated with a trace of sodium ethoxide, and left overnight. The *cyclo*hexen-4-ol so obtained was identified as the α-naphthylurethane, m. p. and mixed m. p. 131°.

Reaction of the cis-*Monotoluene*-p-*sulphonate with Lithium Chloride.*—A solution of the monotoluene-*p*-sulphonate (10 g.) and lithium chloride (7·5 g.) in ethanol (100 c.c.) was refluxed for 17 hours, then concentrated and diluted with water (100 c.c.) to give a strongly acid solution, saturated with salt, and extracted with ether. From the extracts there was obtained 4-chloro*cyclo*hexanol (2·5 g.), b. p. 104—106°/10 mm. Its phenylurethane was separated into two forms by fractional crystallisation, the more abundant form, m. p. 133—134° from light petroleum (b. p. 60—80°), probably being the trans-*compound* (Found: C, 61·45; H, 6·25. $C_{13}H_{12}O_2N_2$ requires C, 61·5; H, 6·35%). The other form, present only in small amount, could not be completely purified; it had m. p. 87—96°, and probably

corresponds to the single phenylurethane of 4-chloro*cyclo*hexanol of m. p. 99° reported by Senderens and Palfray (*Bull. Soc. chim.*, 1928, **43**, 906).

*Action of Sodium Iodide on the Bistoluene-*p*-sulphonates.*—(*a*) The *trans*-bistoluene-*p*-sulphonate (2 g.), sodium iodide (2·6 g.), and acetone (30 c.c.) were refluxed for 14 hours. After cooling, sodium toluene-*p*-sulphonate (1·4 g.) was removed, and the filtrate evaporated to dryness. The pasty solid was extracted with ether, and the extracts then washed with aqueous sodium thiosulphate, dried, and evaporated to a solid (0·2 g.) which was washed with a few drops of ethanol and purified by sublimation at 80°/10^{-4} mm., to give *trans*-1 : 4-di-iodo*cyclo*hexane, m. p. 142—143°. Repetition of the experiment, with ethanol in place of acetone, gave almost identical results.

(*b*) Treatment of the *cis*-bistoluene-*p*-sulphonate (3 g.) with sodium iodide (4 g.) in boiling acetone (50 c.c.) for 19 hours gave an almost theoretical precipitation of sodium toluene-*p*-sulphonate (2·7 g.). After working up in the same way, ether extraction gave a semi-solid product, which on trituration with ethanol left a residue of the *trans*-di-iodide (0·2 g.), which after sublimation at 60°/10^{-4} mm., had m. p. 143° and was identical with that obtained from the *trans*-bistoluene-*p*-sulphonate. The ethanolic mother liquors from the trituration yielded on treatment with water a further quantity of solid, which on fractional crystallisation from ethanol gave another crop of *trans*-di-iodide, and also 5 mg. of *cis*-di-iodo*cyclo*hexane, m. p. 68—69°.

The above experiment was repeated, the solution being heated for 2 hours at 100°. The products yielded 0·4 g. of mixed di-iodides, consisting largely of the *trans*-compound; a trace of the *cis*-isomer was again obtained by following the procedure outlined above.

Action of Sodium Iodide on the trans-*Monotoluene-*p*-sulphonate.*—The derivative (10 g.) was heated with sodium iodide (8 g.) in dry acetone (60 c.c.) in a sealed tube at 100° for 2 hours. After cooling, sodium toluene-*p*-sulphonate (6·7 g.) was removed, and the filtrate worked up to give a yellow oil (8 g.), $n_D^{15°}$ 1·5268. Distillation of a portion, which occurred with some decomposition, gave 4-*iodo*cyclo*hexanol* as a brown viscous oil, b. p. 70—75°/0·002 mm., $n_D^{18°}$ 1·5848 (Found: I, 56·0. $C_6H_{11}OI$ requires I, 56·1%). Non-crystalline products were obtained in attempts to prepare the phenyl- and α-naphthyl-urethanes and the 3 : 5-dinitrobenzoate.

Dehydration of cyclo*Hexane*-1 : 4-*diol.*—The *trans*-diol (15 g.) with anhydrous oxalic acid (80 g.) and water (70 c.c.) was steam-distilled for 2·5 hours. The distillate (1000 c.c.) was saturated with salt and extracted 8 times with ether, but the only product obtained was *cyclo*hexen-4-ol (2·3 g.), identified as the α-naphthylurethane, m. p. 132—133°. Repetition, using concentrated sulphuric acid (20 c.c.) in place of the oxalic acid, gave 4·4 g. of *cyclo*hexen-4-ol.

4-*Chloro*cyclo*hexanol.*—A solution of *cyclo*hexane-1 : 4-diol (114 g.; *cis* + *trans*) in fuming hydrochloric acid (250 c.c.; *d* 1·19) was heated in a strong 3 l.-flask, with wired stopper, at 80—90° for 14 hours. Two layers were formed, and, after cooling, the upper one was extracted twice with chloroform, the extracts being added to the lower layer, which was then washed with water and sodium hydrogen carbonate solution, dried, evaporated, and distilled, to give 4-chloro*cyclo*hexanol (75 g.) as a colourless liquid, b. p. 80—85°/5 mm., $n_D^{18°}$ 1·4964.

Dehydrochlorination of 4-*Chloro*cyclo*hexanol.*—(*a*) 4-Chloro*cyclo*hexanol (10 g.) was refluxed with potassium hydroxide (8 g.) in methanol (40 c.c.) for 4 hours. On cooling, potassium chloride (4·4 g.; theory 5·5 g.) separated and was removed. The methanol solution was poured into water and, after being saturated with salt, the whole was extracted 7 times with ether. The combined extracts were dried (K_2CO_3) and evaporated, and the residue distilled to give a series of liquid fractions (5·5 g.), b. p. 120—220°/760 mm., $n_D^{21°}$ 1·468—1·484. Since a complex mixture was evidently present it was not further investigated.

(*b*) 4-Chloro*cyclo*hexanol (40 g.) and solid potassium hydroxide (50 g.) were heated with stirring in a flask immersed in a bath and fitted with a short Vigreux column. When the bath temperature reached 140° a vigorous reaction set in, the internal temperature rose to 160°, and material, b. p. *ca.* 100°, began to distil, the distillate separating into two layers. The bath temperature was slowly raised to 220° during ½ hour, slow distillation continuing. After cooling, the residue was taken up in water and extracted with ether. Evaporation of the ether gave a dark halogen-free oil (7·3 g.) which was not further investigated. The lower layer of the distillate proved to be water, and was rejected. The upper layer (11 g.) was distilled to give a series of fractions, b. p. 80—170°, $n_D^{20°}$ 1·458—1·466, containing much unsaturated material. This evidently complex mixture was not further investigated.

Reaction of trans-cyclo*Hexane*-1 : 4-*diol with Thionyl Chloride.*—The diol (5 g.) in dry pyridine (50 c.c.) and dry chloroform (50 c.c.) was treated at 0° with a solution of thionyl chloride (5 g., 1 mol.) in dry chloroform (50 c.c.), added during 1 hour with stirring. After 18 hours at ordinary temperature, the product, isolated in the usual way, was obtained on evaporation of the chloroform solution as a horny, pale-brown solid (7·2 g.). A similar result was obtained when the reaction was carried out in boiling chloroform in the absence of pyridine. The product, which contained sulphur but no halogen, was very soluble in chloroform, from which it was precipitated in several fractions, with m. p.s varying, in order, from 110° to 180°. The crude material (1 g.) was refluxed with 5% methanolic potassium hydroxide (30 c.c.) for 6 hours. After cooling, potassium sulphite (0·8 g.) was filtered off and identified. The filtrate was evaporated to dryness, and the residue, on extraction with acetone, gave *trans-cyclo*hexane-1 : 4-diol, m. p. and mixed m. p. 140—141°.

Monobenzoates of cyclo*Hexane*-1 : 4-*diol.*—The *trans*-diol (5 g.) in chloroform (50 c.c.) and pyridine (40 c.c.) was treated at 0° with benzoyl chloride (6 g.) in chloroform (50 c.c.) added during 1 hour with stirring. After being left overnight at ordinary temperature, and worked up in the usual way, the washed and dried chloroform solution was evaporated to a solid residue (8·4 g.) which on crystallisation from benzene–light petroleum (b. p. 60—80°) yielded *trans-cyclo*hexane-1 : 4-diol monobenzoate as prisms (7·4 g.), m. p. 87°. A small quantity of *trans*-dibenzoate, m. p. 149—150°, was isolated from the mother liquors. The *cis*-diol (5 g.), similarly treated, gave a viscous oil (8·3 g.) which on distillation gave a main fraction, b. p. 100° (bath temp.)/10^{-5} mm., $n_D^{17°}$ 1·5408, of the cis-*monobenzoate* (Found: C, 70·6; H, 7·15. $C_{13}H_{16}O_3$ requires C, 70·9; H, 7·3%). A higher-boiling fraction, b. p. 150—210°/10^{-5} mm., yielded some *cis*-dibenzoate, m. p. 110—111°, which was also obtained by further benzoylation of a

sample of the monobenzoate. Treatment of the *cis*-monobenzoate in pyridine solution with toluene-*p*-sulphonyl chloride gave the *cis*-benzoate-toluene-*p*-sulphonate, m. p. 148—150° from methanol–benzene, identical with that obtained by benzoylation of the *cis*-monotoluene-*p*-sulphonate.

Monoacetates of cyclo*Hexane*-1 : 4-*diol*.—The *trans*-diol (5 g.), treated with acetyl chloride (3·4 g.) under exactly the same conditions as those used for the benzoylation, gave a semi-solid product (5·4 g.) which on crystallisation from light petroleum (b. p. 60—80°) gave the monoacetate (2·7 g.) as long needles, m. p. 72°. The mother liquors yielded a quantity of the *trans*-diacetate (0·96 g.), m. p. 102°, together with some less pure monoacetate. The 3 : 5-dinitrobenzoate of the *trans*-monoacetate crystallised from benzene–light petroleum (b. p. 60—80°) in needles, m. p. 146—147° (Dimroth, *loc. cit.*, gives m. p. 145—146°). Similar treatment of the *cis*-diol (10 g.) with acetyl chloride (6·8 g.) gave a crude *cis*-monoacetate (6·4 g.) which could not be induced to crystallise. With 3 : 5-dinitrobenzoyl chloride in pyridine it gave the 3 : 5-dinitrobenzoate-acetate of the *cis*-diol, m. p. 153—155°, undepressed on admixture with the derivative obtained by the action of potassium acetate on the *trans*-monotoluene-*p*-sulphonate (see above). With toluene-*p*-sulphonyl chloride in pyridine, the *cis*-monoacetate gave the *cis*-toluene-*p*-sulphonate-acetate, m. p. 105—106°, identical with that obtained by acetylation of the *cis*-monotoluene-*p*-sulphonate.

4-*Benzoyloxy*cyclo*hexanone*.—The *trans*-monobenzoate (0·6 g.) in acetic acid (20 c.c.) was treated at ordinary temperature with chromium trioxide (0·2 g.) dissolved in water (1 c.c.) and acetic acid (15 c.c.). After standing overnight, the solution was diluted with ether, washed with sodium hydrogen carbonate solution, dried, and evaporated to a solid. The 4-benzoyloxy*cyclo*hexanone crystallised from light petroleum in plates (0·5 g.), m. p. 62° (Found : C, 73·5; H, 6·2. Calc. for $C_{13}H_{14}O_3$: C, 73·2; H, 6·5%) [Dimroth (*Ber.*, 1942, **75**, 317) gives m. p. 63—64°]. It gave a *semicarbazone*, leaflets, m. p. 195—196°, from light petroleum (b. p. 100—120°) (Found : C, 60·6; H, 6·1. $C_{14}H_{17}O_3N_3$ requires C, 61·1; H, 6·2%), and a 2 : 4-dinitrophenylhydrazone, m. p. 160—161° (Found : N, 14·2. Calc. for $C_{19}H_{18}O_6N_4$: N, 14·1%).

The benzoyloxy-ketone was also obtained, and identified as the 2 : 4-dinitrophenylhydrazone, by similar oxidation of the *cis*-monobenzoate of *cyclo*hexane-1 : 4-diol.

We are indebted to Monsanto Chemicals Ltd., for the award of a Research Scholarship to one of us (P. A. R.), during the tenure of which the work described in this and the following paper was carried out.

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[*Received, April 5th*, 1948.]

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76. *Alicyclic Glycols. Part III.* 4-*Hydroxymethyl*cyclo*hexanol*.

By L. N. OWEN and P. A. ROBINS.

The synthesis of 4-*hydroxymethyl*cyclo*hexanol* (I) from *p*-hydroxybenzoic acid is described. From the *cis*- and *trans*-forms, several mono- and di-substituted derivatives have been obtained, and, by making use of the greater reactivity of the primary hydroxyl group, structurally isomeric compounds such as the 1-*benzoate*-ω-*toluene*-p-*sulphonate* and ω-*benzoate*-1-*toluene*-p-*sulphonate* have been prepared, their structures proved, and their properties studied. The difference in behaviour between primary and secondary toluene-*p*-sulphonyl groups has been demonstrated in several reactions. On treatment with methanolic alkali, a tosyloxy-group in the primary position is replaced, to give the methyl ether, whilst one in the secondary position is eliminated, with formation of an ethylenic linkage (cf. Parts I and II). Smooth replacement of the primary tosyloxy-group by acetoxy-, chlorine, and iodine has also been observed, in contrast to the results obtained with secondary toluene-*p*-sulphonyl compounds. The configuration of the *trans*-form of the glycol (I) has been proved by relating it to the *trans*-forms of 4-hydroxy*cyclo*hexanecarboxylic acid and 4-hydroxy*cyclo*hexanol.

*cyclo*HEXANE-1 : 4-DIOL, the simplest analogue of 1 : 4-terpin, has been discussed in Part II (preceding paper). The present account is concerned with the homologue, 4-*hydroxymethyl*-cyclo*hexanol* (I), a compound which is similarly related to 1 : 8-terpin (II), and also of interest because it contains both a primary and a secondary hydroxyl group.

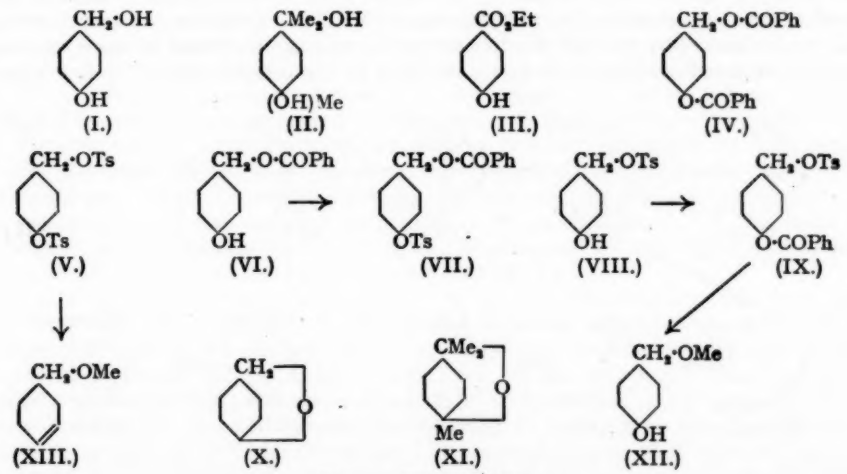
The glycol was synthesised from *p*-hydroxybenzoic acid, and it was necessary to make a preliminary study of the hydrogenation of this acid and of its ethyl ester under various conditions. Balas and Srôl (*Coll. Czech. Chem. Comm.*, 1929, **1**, 658) and Edson (*J. Soc. Chem. Ind.*, 1934, **53**, 138T) reported that reduction of the acid proceeded slowly in aqueous or ethanolic solution over a platinum catalyst at ordinary pressure to give poor yields of 4-hydroxy*cyclo*hexanecarboxylic acid, simultaneous hydrogenolysis leading to the formation of *cyclo*hexanecarboxylic acid. We have confirmed these observations, and have failed to effect any marked improvement by increasing the pressure to 100 atm. Attempted reduction of an alcoholic solution of the potassium salt of the hydroxy-acid at 150° and 125 atm., over Raney nickel, resulted only in the formation of phenol; this decarboxylation was found to occur merely on heating the alcoholic solution of the salt to 150°, and it is evidently related to the production of *cyclo*hexanol in attempted reduction of the acid, under somewhat similar conditions, by Ipatieff and Razuvaieff (*Ber.*, 1926, **59**, 306) and Levin and Pendergrass (*J. Amer. Chem. Soc.*, 1947, **69**, 2436). Mitsui

(*Mem. Coll. Sci. Kyoto Imp. Univ.*, 1935, *A*, **18**, 329) claimed good results for the hydrogenation of ethyl *p*-hydroxybenzoate over a supported nickel catalyst, though Martin and Robinson (*J.*, 1943, 491) found Raney nickel unsuitable, and recommended palladium on strontium carbonate (cf. Hardegger, Heuser, and Blank, *Helv. Chim. Acta*, 1946, **29**, 477). In our hands, however, Raney nickel has been quite satisfactory, and has given ethyl 4-hydroxy*cyclo*hexanecarboxylate (III) in consistently good yield.

The carbethoxy-group in (III) was reduced both by the Bouveault–Blanc method (yield 60%, with sodium and ethanol) and by hydrogenation in alcoholic solution over copper chromite at 250° and 200 atm. With the latter method, however, it was impossible to obtain consistent results; of seven experiments, all carried out under apparently identical conditions, one gave a yield of 61%, and two of about 5%, whilst the remainder gave practically none of the desired material, but mainly 4-methyl*cyclo*hexanol. This hydrogenolysis is similar to the observation by Adkins (*J. Amer. Chem. Soc.*, 1932, **54**, 4678) that hydrogenation of ethyl 2-hydroxy*cyclo*hexanecarboxylate over copper chromite gave a 92% yield of 2-methyl*cyclo*hexanol, but the latter result is not unexpected, since the primary reduction product is 2-hydroxy*cyclo*hexylcarbinol and it is known that 1 : 2- and 1 : 3- glycols readily undergo hydrogenolysis under these conditions. Similar behaviour by a 1 : 5-glycol, however, is surprising.

The product was a viscous liquid which partly crystallised. The solid portion, amounting to *ca.* 30%, was subsequently proved, as described later, to be trans-4-*hydroxymethyl*cyclo*hexanol*; the residual liquid, purified by distillation, contained the cis-*form*, and was characterised as the *bisphenylurethane*.

The *trans*-glycol gave a *dibenzoate* (IV) and a *bistoluene*-p-*sulphonate* (V); with one mol. of benzoyl chloride it gave the ω-*monobenzoate* (VI) as a liquid, which reacted with toluene-*p*-sulphonyl chloride to give the crystalline ω-*benzoate*-1-*toluene*-ρ-*sulphonate* (VII); similarly, one mol. of toluene-*p*-sulphonyl chloride yielded a crude ω-monotoluene-*p*-sulphonate (VIII) which could not be purified, but on benzoylation gave the 1-*benzoate*-ω-*toluene*-p-*sulphonate* (IX). The *cis*-glycol, probably not stereochemically pure, was also converted into the corresponding derivatives, but only the *bistoluene*-p-*sulphonate* was obtained in crystalline form. The structures assigned to the mixed derivatives (VII) and (IX), based on the expected preferential reactivity of the primary hydroxyl group, were confirmed by evidence which is considered at the end of this paper.



(Ts = *p*-$CH_3 \cdot C_6H_4 \cdot SO_2$.)

1 : 4-*endo*Oxymethylene*cyclo*hexane (X), which is not described in the literature, may be considered to be the simple analogue of 1 : 8-cineole (XI) in the same way as 1 : 4-epoxy*cyclo*hexane is related to 1 : 4-cineole (see Part II). Since it appeared from the experiments described in Part II that a toluene-*p*-sulphonyl group in a secondary position, on treatment with alkali, gave an unsaturated product rather than an ether or anhydro-compound, it was clear that the behaviour of the primary toluene-*p*-sulphonyl derivative (IX) would be of more interest than that of the structural isomer (VII), which would probably give only 4-hydroxymethyl*cyclo*hexene. Whereas, however, the formation of the 1 : 4-epoxide, had it occurred, would

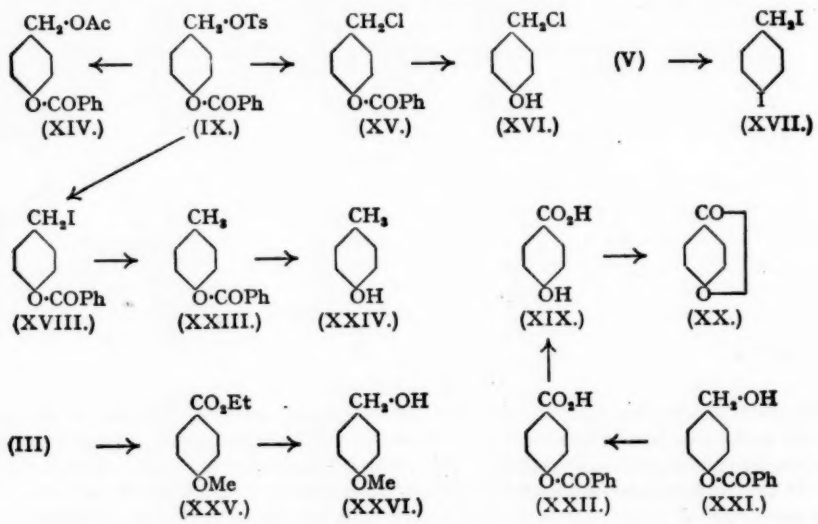
presumably have been easier from the *trans*-monotoluene-*p*-sulphonyl derivative of *cyclo*hexane-1 : 4-diol, in the present case it would be expected that ring formation would occur most readily from the *cis*-primary monotoluene-*p*-sulphonate, since the inversion accompanying removal of the toluene-*p*-sulphonyl group would not reverse the configuration at C_4. Both the *cis*- and *trans*-forms of (IX), however, reacted with methanolic potassium hydroxide to give 4-*methoxymethyl*cyclo*hexanol* (XII), indicating that ether formation had occurred intermolecularly with the solvent, rather than intramolecularly with the hydroxyl group at C_1.

The difference in reactivity between the primary and secondary toluene-*p*-sulphonyl groups was well demonstrated by reaction of the bistoluene-*p*-sulphonate (V) with methanolic potassium hydroxide, whereby the primary group was replaced to form an ether, whilst the secondary was eliminated with the introduction of a double bond, the product being 4-*methoxymethyl*cyclo*hexene* (XIII).

The *trans*-1-benzoate-ω-toluene-*p*-sulphonate (IX) reacted with methanolic potassium acetate to yield the 1-*benzoate*-ω-*acetate* (XIV), only a trace of acid being liberated. The replacement thus proceeds normally, in striking contrast to the behaviour of a secondary toluene-*p*-sulphonyl group under such conditions (cf. Part II).

Two experiments were carried out on the reaction of the toluene-*p*-sulphonyl-groups with lithium chloride. The *cis*-isomer of (IX) gave the *benzoate* (XV) of *cis*-4-chloromethyl*cyclo*hexanol (XVI) as an oil, which after removal of the benzoyl group by cautious saponification was characterised as the α-*naphthylurethane*. Similarly, the *trans*-ω-monotoluene-*p*-sulphonate (VIII) gave trans-4-*chloromethyl*cyclo*hexanol* (XVI), characterised as the *phenylurethane*, and the α-*naphthylurethane*. The *cis*- and *trans*-forms of the chloride (XVI) were also obtained from the corresponding forms of the glycol (I) by reaction with fuming hydrochloric acid, the urethanes being respectively identical with those described above.

It was shown in Parts I and II that a secondary toluene-*p*-sulphonyloxy-group can be replaced by iodine, though in rather poor yield, and the effect of sodium iodide in acetone solution on both *cis*- and *trans*-bistoluene-*p*-sulphonates (V) was therefore investigated. In each case an almost theoretical amount of sodium toluene-*p*-sulphonate was precipitated, with formation of the rather unstable 4-*iodomethyl*cyclo*hexyl iodide* (XVII). The product was a liquid, the physical properties of which were almost identical in the two preparations, so it was not possible to determine to what extent inversion had occurred at C_1 during the reaction. The *trans*-1-benzoate-ω-toluene-*p*-sulphonate (IX) reacted with sodium iodide in acetone to give a good yield of trans-4-*iodomethyl*cyclo*hexyl benzoate* (XVIII). Difference in reactivity between a primary and a secondary toluene-*p*-sulphonyl group was again evident in these reactions, and from the accumulated evidence it is now clear that at the temperature of boiling acetone the



precipitation of sodium toluene-*p*-sulphonate from a primary group is complete after 2—3 hours, whilst for a secondary group 12 hours or longer are necessary. In the latter case, decomposition

of the product invariably occurs, and better results with a secondary toluene-*p*-sulphonyl group are usually obtained by carrying out the reaction in a sealed tube at 100° for 2—3 hours.

The allocation of a *trans*-configuration to the solid form of the glycol (I) was subsequently confirmed by relating the compound to particular stereoisomers both of 4-hydroxy*cyclo*hexanecarboxylic acid and of 4-methyl*cyclo*hexanol. This hydroxy-acid (XIX) is known in two forms, m. p.s 120° and 152°, and the latter, despite its higher m. p. and lower solubility, was assigned the *cis*-configuration by Balas and Srôl (*loc. cit.*) on the grounds of the formation from it of a lactone (XX), m. p. 109—110°. Perkin (*J.*, 1904, **85**, 430) had earlier observed that dry distillation of the lower-melting form gave a solid product (m. p. not stated) which was said not to be a lactone; he had therefore assumed this acid, m. p. 120°, to be the *trans*-form. It has now been found, however, that this solid product described by Perkin is identical with the lactone described by Balas and Srôl. The previous evidence of configuration, which would in any event appear to have been rather dubious in view of the very vigorous conditions of lactonisation, is therefore nullified, but we have also observed that solution of the lactone in cold aqueous alkali, followed by acidification and extraction with ether, yields the acid, m. p. 152°. Since the opening of a lactone ring under mild conditions, considered as a simple saponification of a carboxylic ester, must occur without inversion, it follows that the acid, m. p. 152°, has the *cis*-configuration.

The pure *trans*-acid was converted into its ethyl ester and reduced by the Bouveault–Blanc method, but the glycol obtained was a mixture of stereoisomers, partial inversion having occurred, not unexpectedly, during the process. Attempts to oxidise the solid glycol preferentially at the primary hydroxyl group, in an endeavour to obtain one of the stereoisomeric hydroxy-acids, were not successful, but by cautious saponification of the *trans*-dibenzoate (IV) with one mol. of sodium hydroxide in aqueous acetone, the secondary *monobenzoate* (XXI) was obtained in good yield and identified by conversion of a sample into the ω-benzoate-1-toluene-*p*-sulphonate already described. Oxidation of (XXI) with chromic acid gave the *benzoate* (XXII) of 4-hydroxy*cyclo*hexanecarboxylic acid. Attempts to prepare this benzoate from either of the hydroxy-acids were unsuccessful, owing to their resistance to benzoylation; furthermore, the derivative itself was very resistant to saponification, but on refluxing for 24 hours with 20% methanolic potassium hydroxide it gave the *trans*-acid (XIX), m. p. 120°. A control experiment showed that the *cis*-acid, m. p. 152°, was not converted into the *trans*- under the vigorous treatment with alkali; isolation of the *trans*-acid therefore proves conclusively the *trans*-configuration of the original solid glycol.

Correlation between the glycol and the stereoisomeric forms of 4-methyl*cyclo*hexanol was readily achieved by hydrogenation of the *trans*-4-iodomethyl*cyclo*hexyl benzoate (XVIII) in methanol, with a platinum catalyst, to the trans-*benzoate* (XXIII) of 4-methyl*cyclo*hexanol, m. p. 34—35°. [The liquid benzoate of 4-methyl*cyclo*hexanol described by Zaki (*J.*, 1932, 1184) was probably a mixture of stereoisomers.] This compound, in contrast to the benzoate (XXII), readily underwent alcoholysis by the Zemplén method, and the resulting 4-methyl*cyclo*hexanol (XXIV) was identified as the *trans*-form by conversion into the phenylurethane and the α-naphthylurethane,. The allocation of the *cis*- and *trans*-configurations to the 4-methyl*cyclo*hexanols was previously based on physical properties (Skita and Faust, *Ber.*, 1931, **64**, 2878), but the present work has confirmed these earlier conclusions by relating the *trans*-alcohol, through the *trans*-glycol (I), to the *trans*-hydroxy-acid (XIX).

Confirmation of the structures assigned to the structurally isomeric benzoyl-toluene-*p*-sulphonyl derivatives (VII) and (IX) is afforded by the following observations. Methylation with methyl iodide and silver oxide of ethyl (*cis* + *trans*)-4-hydroxy*cyclo*hexanecarboxylate (III) afforded the *methyl ether* (XXV), which on reduction by the Bouveault–Blanc method gave (cis + trans)-4-*hydroxymethyl*cyclo*hexyl methyl ether* (XXVI) as a liquid, the α-naphthylurethane of which was separated by fractional crystallisation into two *stereoisomers*, cis(?)-, m. p. 95—96°; and *trans*(?) m. p. 113—114°. Neither of these derivatives was identical with the *α-naphthylurethane* obtained from the methyl ether (XII), which therefore must be structurally different, and consequently has the formula assigned to it; it follows that the toluene-*p*-sulphonyl derivative (IX) is correctly formulated. Independent evidence is also afforded by the fact that the monobenzoate (XXI), which on toluene-*p*-sulphonation gives (IX), must have a free primary hydroxyl group, since it is oxidised to the benzoyloxy-acid (XXII).

Experimental.

(Light petroleum, unless otherwise stated, refers to the fraction, b. p. 40—60°.)

Attempted Hydrogenation of Potassium p-*Hydroxybenzoate.*—*p*-Hydroxybenzoic acid (50 g.) and potassium hydroxide (24·5 g.) were dissolved in ethanol (300 c.c.) and stirred with hydrogen in the

presence of Raney nickel (10 g.) at 150°/150 atm. for 24 hours. After removal of solvent from the filtered solution, the residue was acidified with sulphuric acid and extracted with ether. Distillation of the product gave phenol (31·3 g.), m. p. 40°.

Decarboxylation of p-*Hydroxybenzoic Acid.*—The acid (5 g.), potassium hydroxide (2·5 g.), and ethanol (30 c.c.), heated for 24 hours at 150° and worked up as above, gave phenol (3 g.), m. p. 41°.

Ethyl 4-*Hydroxy*cyclo*hexanecarboxylate.*—Ethyl *p*-hydroxybenzoate (70 g., m. p. 112—114°) in ethanol (200 c.c.) was hydrogenated at 150°/85 atm. (initial pressure at room temperature) for 20 hours over Raney nickel (5 g.). The hydrogenated ester (55 g.) obtained by distillation of the product had b. p. 142—145°/15 mm., $n_D^{18°}$ 1·4673, and was mainly the *trans*-form, since on saponification with boiling 10% aqueous potassium hydroxide it gave a crude solid acid, m. p. 110—112°, raised on recrystallisation from ethyl acetate to 119·5° (*trans*-4-hydroxy*cyclo*hexanecarboxylic acid has m. p. 120°).

4-*Hydroxymethyl*cyclo*hexanol* (I).—(*a*) To a solution of ethyl 4-hydroxy*cyclo*hexanecarboxylate (172 g.) in anhydrous ethanol (1500 c.c.), contained in a 3 l. flask fitted with a large reflux condenser, was added sodium (138 g.). The reaction was allowed to proceed as vigorously as possible without mechanical loss, some cooling being necessary in the early stages. Finally, the mixture was heated on the steam-bath until all the sodium had dissolved (*ca.* 3 hours). After addition of water (200 c.c.), most of the alcohol was removed under reduced pressure. The residue, diluted with more water (400 c.c.), was continuously extracted with ether for 40 hours. Evaporation of the dried extracts gave an oil (106 g.) which partly solidified on treatment with acetone (50 c.c.) and ether (150 c.c.). The solid material was triturated with more acetone (50 c.c.), washed with a little ether, and recrystallised from ethyl acetate to give trans-4-*hydroxymethyl*cyclo*hexanol* in prisms, m. p. 103° (Found: C, 64·5; H, 10·6. $C_7H_{14}O_2$ requires C, 64·6; H, 10·8%). The combined mother liquors were diluted with ether until cloudy; the small quantity of precipitated solid was removed, and the filtrate evaporated to an oil (70 g.), which on distillation gave 56 g., b. p. 135—147°/3 mm., $n_D^{14°}$ 1·4910, of (mainly) *cis*-4-hydroxymethyl*cyclo*hexanol (Found: C, 65·1; H, 10·5). With excess of phenyl *iso*cyanate for 24 hours, it gave a *bisphenylurethane*, crystallising from benzene, m. p. 179—181° (Found: C, 68·2; H, 6·7. $C_{21}H_{24}O_4N_2$ requires C, 68·4; H, 6·6%). 4-Hydroxy*cyclo*hexanecarboxylic acid (18·9 g.) was recovered after acidification of the original aqueous residues.

(b) Ethyl 4-hydroxy*cyclo*hexanecarboxylate (50 g.) in ethanol (100 c.c.), with copper chromite catalyst (10 g., containing barium, prepared according to *Org. Synth.*, Coll. Vol. II, p. 142), was sealed in an autoclave under hydrogen at 125 atm. The autoclave was heated as rapidly as possible to 250°, the pressure then being 210 atm., whereupon stirring was begun. Pressure rose rapidly to 280 atm., and then fell slowly during 2 hours to 186 atm. Stirring and heating were then discontinued. Removal of solvent from the cooled and filtered mixture gave 23 g. of the glycol, b. p. 156—165°/15 mm., which was separated as above into the solid (7 g.) and liquid (14 g.) forms. Repetition of this hydrogenation failed to give comparable results, the products obtained containing much *p*-cresol and 4-methyl*cyclo*hexanol.

Derivatives of the trans-*Glycol.*—(*a*) With excess of benzoyl chloride in pyridine it gave the trans-*dibenzoate*, plates from aqueous methanol, m. p. 80—81° (Found: C, 74·5; H, 6·5. $C_{21}H_{22}O_4$ requires C, 74·5; H, 6·55%), and with excess of toluene-*p*-sulphonyl chloride in pyridine, the trans-*bistoluene*-p-*sulphonate* was obtained, crystallising from methanol in needles, m. p. 94° (Found: C, 57·4; H, 5·9. $C_{21}H_{24}O_6S_2$ requires C, 57·5; H, 6·0%).

(*b*) Treatment of the *trans*-glycol (5 g.) in pyridine (40 c.c.) and pure chloroform (25 c.c.) with a solution of benzoyl chloride (5 g.) in chloroform (40 c.c.), added with stirring at 0° during 1 hour, followed by standing overnight at room temperature, gave a liquid product which on fractional distillation gave the trans-*ω-monobenzoate* (6·2 g.) as a viscous oil, b. p. 95° (bath temp.)/10^{-4} mm., $n_D^{18°}$ 1·5346 (Found: C, 71·45; H, 8·0. $C_{14}H_{18}O_3$ requires C, 71·35; H, 7·75%). The higher-boiling material (1·2 g.), b. p. 120—125° (bath temp)/10^{-5} mm., solidified, and was the dibenzoate, m. p. 80—81°, identical with that described above. Treatment of the monobenzoate with toluene-*p*-sulphonyl chloride in pyridine gave the trans-*ω-benzoate*-1-*toluene*-p-*sulphonate*, which crystallised from benzene–light petroleum (b. p. 60—80°) in stout needles, m. p. 82—83° (Found: C, 64·9; H, 6·1. $C_{21}H_{24}O_5S$ requires C, 64·9; H, 6·2%).

(*c*) The *trans*-glycol (5 g.) in pyridine (40 c.c.) was treated at 0° with toluene-*p*-sulphonyl chloride (8·8 g.) added in small portions during 1 hour. After standing at room temperature overnight, the product was isolated as an oil, which on solution in methanol and cooling to 0° deposited a small quantity of the *trans*-bistoluene-*p*-sulphonate. Evaporation of the methanol then left a crude *ω*-monotoluene-*p*-sulphonate, which failed to crystallise and could not be distilled without decomposition; it was therefore dissolved in pyridine and treated with excess of benzoyl chloride, and gave the trans-1-*benzoate*-*ω*-*toluene*-p-*sulphonate* (11·1 g.) as long prisms from ethanol, m. p. 110—111° (Found: C, 65·1; H, 6·3. $C_{21}H_{24}O_5S$ requires C, 64·9; H, 6·2%).

Derivatives of the cis-*Glycol.*—(*a*) Treatment of the glycol (5 g.) dissolved in pyridine (50 c.c.) with excess of benzoyl chloride (15 g.) during 1·5 hours at 0° gave a deep purple mixture which was left at room temperature for 40 hours and then worked up to give an oil (18·1 g.). Distillation gave a lower fraction (5·3 g.) of a brown viscous nitrogenous oil, b. p. 85° (bath temp.)/5 × 10^{-4} mm., and a second fraction (9·1 g.) of a yellow nitrogen-free oil, b. p. 140—160° (bath temp.)/5 × 10^{-4} mm., which on redistillation gave the cis-*dibenzoate*, 7·5 g., b. p. 140—150° (bath temp.)/5 × 10^{-4} mm., $n_D^{15°}$ 1·5562, as an almost colourless viscous oil (Found: C, 74·95; H, 6·5. $C_{21}H_{22}O_4$ requires C, 74·5; H, 6·55%).

(*b*) The cis-*bistoluene*-p-*sulphonate*, prepared by reaction with excess of toluene-*p*-sulphonyl chloride in pyridine, crystallised from methanol in needles, m. p. 98·5°, depressed to 84° on admixture with the *trans*-isomer (Found: C, 57·6; H, 5·9. $C_{21}H_{24}O_6S_2$ requires C, 57·5; H, 6·0%).

(*c*) Treatment of the *cis*-glycol with 1 mol. of benzoyl chloride under the same conditions as those used for the preparation of the *trans*-monobenzoate gave the cis-*ω-monobenzoate* as a colourless viscous oil, b. p. 105° (bath temp.)/5 × 10^{-5} mm., $n_D^{20°}$ 1·5332 (Found: C, 71·2; H, 7·85. $C_{14}H_{18}O_3$ requires C, 71·75; H, 7·75%).

(*d*) The *cis*-glycol (10 g.) was treated in pyridine–chloroform solution with toluene-*p*-sulphonyl chloride (14·6 g.) under the usual conditions for the preparation of the mono-derivative. After being

left at room temperature for 24 hours the mixture was again cooled to 0°, and treated with benzoyl chloride (13·5 g.) in chloroform (50 c.c.). The product was isolated as a dark red oil (30 g.) which failed to solidify. It was decolourised by filtration of a solution in benzene–light petroleum through a column of activated alumina, but the *cis*-1-benzoate-ω-toluene-*p*-sulphonate failed to crystallise and could not be purified by distillation (Found: C, 68·0; H, 7·1. Calc. for $C_{21}H_{24}O_5S$: C, 64·9; H, 6·2%).

Action of Alkali on (IX).—(*a*) The *trans*-1-benzoate-ω-toluene-*p*-sulphonate (11 g.) was heated under reflux for 3 hours with 5% methanolic potassium hydroxide (100 c.c.). On cooling, and addition of ether, a crystalline mass of potassium toluene-*p*-sulphonate separated and was removed. The filtrate was neutralised with carbon dioxide, again filtered, concentrated to small bulk, and diluted with water. Extraction with ether gave trans-4-*methoxymethylcyclohexanol* (1·5 g.), b. p. 114—116°/18 mm., $n_D^{18°}$ 1·4652 (Found: C, 66·5; H, 11·3. $C_8H_{16}O_2$ requires C, 66·65; H, 11·2%). The *α-naphthylurethane* crystallised from light petroleum (b. p. 60—80°) in fine needles, m. p. 117—118° (Found: C, 72·95; H, 7·3. $C_{19}H_{23}O_3N$ requires C, 72·8; H, 7·4%).

(*b*) The crude *cis*-1-benzoate-ω-toluene-*p*-sulphonate (25 g.) was heated under reflux for 6 hours with 5% methanolic potassium hydroxide (200 c.c.). Working up as before gave a liquid product (7 g.), b. p. 124—128°/18 mm, $n_D^{19°}$ 1·4673, which was presumably mainly *cis*-4-methoxymethyl*cyclo*hexanol, although good analytical figures could not be obtained (Found: C, 67·3, 67·6; H, 11·2, 11·1. Calc. for $C_8H_{16}O_2$: C, 66·65; H, 11·2%). The product reacted readily with α-naphthyl *iso*cyanate, but a solid urethane could not be obtained.

*Action of Alkali on the Bistoluene-*p*-sulphonate* (V).—The *trans*-bistoluene-*p*-sulphonate (15 g.) and 5% methanolic potassium hydroxide (150 c.c.) were heated under reflux for 2 hours. After cooling, and removal of precipitated potassium toluene-*p*-sulphonate, the solution was concentrated to 20 c.c., diluted with ether, washed twice with water, dried, and evaporated to an oil, which on distillation gave 4-*methoxymethyl*cyclo*hexene*, 1·5 g., b. p. 86—88°/100 mm., $n_D^{23°}$ 1·4519 (Found: C, 76·6; H, 11·5. $C_8H_{14}O$ requires C, 76·15; H, 11·2%). The methanolic distillate contained unsaturated material, and a further small quantity of the methyl ether was recovered from it by dilution with water and extraction with ether; its evident volatility probably accounts for the poor yield.

Reaction of (IX) *with Potassium Acetate.*—The *trans*-1-benzoate-ω-toluene-*p*-sulphonate (3 g.) and potassium acetate (3 g.) in ethanol (30 c.c.) were refluxed for 3 hours. Water and chloroform were then added, and the lower layer separated. The aqueous layer contained only a trace of acid, requiring only 0·5 c.c. of N-sodium hydroxide for neutralisation to phenolphthalein. The chloroform layer was dried and evaporated to a solid residue (2·33 g.) of the trans-1-*benzoate-ω-acetate* (XIV) which crystallised from aqueous methanol in prisms, m. p. 78—79° (Found: C, 69·45; H, 7·3. $C_{16}H_{20}O_4$ requires C, 69·55; H, 7·3%).

Reaction of (IX) *with Lithium Chloride.*—The crude *cis*-1-benzoate-ω-toluene-*p*-sulphonate (6·4 g.) in ethanol (30 c.c.) was refluxed with lithium chloride (3 g.) for 5·5 hours. After concentration and dilution with water, ether extraction gave an oil (3·8 g.), which on distillation yielded the *benzoate* of *cis*-4-chloromethyl*cyclo*hexanol as a colourless oil, 2·9 g., b. p. 127—130°/0·3 mm., $n_D^{21°}$ 1·5288 (Found: C, 66·1; H, 6·9. $C_{14}H_{17}O_2Cl$ requires C, 66·5; H, 6·8%). Saponification of this compound (1 g.) by refluxing for 0·5 hour with 5% methanolic potassium hydroxide (20 c.c.) gave *cis*-4-chloromethyl*cyclo*hexanol as an oil (0·58 g.) which was characterised as the *α-naphthylurethane*, needles from light petroleum (b. p. 100—120°), m. p. 123° (Found: C, 68·05; H, 6·2. $C_{18}H_{20}O_3NCl$ requires C, 68·0; H, 6·3%).

Reaction of (VIII) *with Lithium Chloride.*—Crude *trans*-ω-monotoluene-*p*-sulphonate (14 g., prepared by toluene-*p*-sulphonation of the *trans*-glycol) was refluxed in ethanol (50 c.c.) for 7·5 hours with lithium chloride (9 g.). The product was a yellow oil (11·7 g.) which on distillation furnished trans-4-*chloromethyl*cyclo*hexanol* as a colourless oil, b. p. 98—99/4 mm., $n_D^{16°}$ 1·4931 (Found: C, 55·9; H, 9·0. $C_7H_{13}OCl$ requires C, 56·6; H, 8·8%). The *phenylurethane* separated from light petroleum (b. p. 60—80°) in needles, m. p. 129—130° (Found: C, 62·9; H, 6·6. $C_{14}H_{18}O_2NCl$ requires C, 62·8; H, 6·8%). The *α-naphthylurethane* crystallised from light petroleum (b. p. 100—120°) in leaflets, m. p. 183—184° (Found: N, 4·5. $C_{18}H_{20}O_2NCl$ requires N, 4·4%).

4-Chloromethylcyclohexanol from the Glycol.—(*a*) The *trans*-glycol (10 g.) dissolved in fuming hydrochloric acid (20 c.c., *d* 1·19) was heated in a sealed tube at 80—90° for 6 hours, during which time two layers were formed. The upper layer was diluted with ether, washed with sodium hydrogen carbonate, dried, evaporated, and distilled to give *trans*-4-chloromethyl*cyclo*hexanol, 8·9 g., b. p. 98—100°/3 mm., $n_D^{23°}$ 1·4910, $n_D^{33°}$ 1·4884, characterised as the phenylurethane, m. p. 129—130°, identical with that described above.

(*b*) The *cis*-glycol (15 g.), similarly treated, gave cis-4-*chloromethyl*cyclo*hexanol*, 11·5 g., b. p. 106—112°/12 mm., $n_D^{14°}$ 1·4940 (Found: C, 56·8; H, 8·6. $C_7H_{13}OCl$ requires C, 56·55; H, 8·8%), which gave an α-naphthylurethane, m. p. 122°, identical with that obtained by the other route.

*Action of Sodium Iodide on the Bistoluene-*p*-sulphonate* (V).—(*a*) The *cis*-bistoluene-*p*-sulphonate (3 g.) and sodium iodide (4 g.) in dry acetone (20 c.c.) were heated in a sealed tube at 100° for 1·5 hours. The product, isolated in the usual way, on distillation gave 4-*iodomethylcyclohexyl iodide* (1·3 g.) as a deep yellow liquid, b. p. 40—50° (bath temp.)/10^{-4} mm., $n_D^{22°}$ 1·6209 (Found: I, 72·6. $C_7H_{13}I_2$ requires I, 72·5%).

(*b*) The *trans*-bistoluene-*p*-sulphonate (3 g.) on reaction with sodium iodide (4 g.) as for the *cis*-compound, also gave 4-iodomethyl*cyclo*hexyl iodide (2·5 g.), $n_D^{22°}$ 1·6180, identical in properties with that obtained from the *cis*-bis-*p*-toluenesulphonate.

*Action of Sodium Iodide on the Benzoate-toluene-*p*-sulphonate* (IX).—The *trans*-1-benzoate-ω-toluene-*p*-sulphonate (5 g.) and sodium iodide (3·3 g.) in acetone (50 c.c.) were heated under reflux for 5 hours. After addition of ether, the filtered solution was washed with aqueous sodium thiosulphate, dried, and evaporated to a solid residue (3 g.) of trans-4-*iodomethylcyclohexyl benzoate*, m. p. 49—53°, raised to 56—57° by sublimation at 70°/10^{-4} mm., or by recrystallisation from aqueous methanol (Found: C, 48·9; H, 4·85. $C_{14}H_{17}O_2I$ requires C, 48·85; H, 5·0%).

4-Hydroxycyclohexanecarboxylic Acid.—(*a*) *p*-Hydroxybenzoic acid (5 g.) in ethanol (30 c.c.) was shaken with hydrogen in the presence of Adams's platinum catalyst for a total of 28 hours, by which time

the theoretical volume of gas (2·6 l.) had been absorbed, the catalyst being renewed at intervals when the rate of absorption became slow. Crystallisation of the product from acetone gave *cis*-4-hydroxy-*cyclo*hexanecarboxylic acid (2·7 g.), m. p. 152° From the mother liquors a small quantity of the *trans*-isomer, m. p. 120°, was obtained.

(*b*) Ethyl 4-hydroxy*cyclo*hexanecarboxylate (65 g.) was saponified by refluxing with 20% aqueous potassium hydroxide (400 c.c.) for 3 hours. After removal of unchanged ester by extraction with ether, the aqueous solution was acidified and constantly extracted with ether for several hours, to yield a solid acid (51 g.). This on crystallisation from acetone gave mainly the *trans*-acid, m. p. 120°.

Lactone of 4-*Hydroxy*cyclo*hexanecarboxylic Acid* (XX).—The *trans*-acid, m. p. 120° (4 g.), was distilled at atmospheric pressure over a free flame. The distillate, b. p. 250—270°, largely solidified, and unlike the acid was readily soluble in a small amount of boiling ether, from which it separated in leaflets, m. p. 108—112°, unchanged on recrystallisation (Bàlas and Srôl, *loc. cit.*, give m. p. 109—110° for the lactone prepared from the *cis*-acid). This lactone dissolved slowly in cold 10% aqueous potassium hydroxide solution, and acidification of the solution, followed by saturation with salt and continuous extraction with ether, gave an extract which on cooling deposited prisms of the *cis*-acid, m. p. 152—153°. Concentration of the extract to small bulk gave a further quantity, m. p. 147—149°, raised to 152° by recrystallisation from ethyl acetate. Evaporation of the mother liquors to dryness gave no indication of the lower melting (*trans*) form.

Reduction of Ethyl trans-4-*Hydroxy*cyclo*hexanecarboxylate*.—The ester (21 g.), b. p. 143—144°/12 mm., $n_D^{14°}$ 1·4678, prepared by esterification of the pure *trans*-acid with ethanol and sulphuric acid, was reduced with sodium and alcohol as previously described to give a semi-solid product (13 g.) which on crystallisation from acetone gave the *trans*-glycol (I) (4·5 g.), m. p. 102°. The remaining material, recovered from the mother liquors, failed to crystallise and, in the light of the earlier experiments, evidently consisted largely of the *cis*-glycol.

Partial Saponification of the Dibenzoate (IV).—To a solution of the *trans*-dibenzoate (8·16 g.) in acetone (80 c.c.), N-aqueous sodium hydroxide (25 c.c.) was added. After being shaken at room temperature for 48 hours, the solution was no longer alkaline to phenolphthalein and it was diluted with water and extracted with chloroform. Removal of solvent from the dried extracts, and distillation of the resulting oil, gave the slightly impure trans-1-*monobenzoate* (XXI), 3·5 g., b. p. 120—130° (bath temp.)/10^{-5} mm., $n_D^{18°}$ 1·4351 (Found: C, 72·5; H, 7·75. $C_{14}H_{18}O_3$ requires C, 71·75; H, 7·75%). The residue in the distillation flask (0·7 g.) crystallised, and was identified as unchanged *trans*-dibenzoate, m. p. 80° after crystallisation from methanol. The monobenzoate, treated with toluene-*p*-sulphonyl chloride in pyridine, gave the *trans*-1-benzoate-*ω*-toluene-*p*-sulphonate (IX), m. p. 110—111°, identical with that previously obtained.

Benzoate of trans-4-*Hydroxy*cyclo*hexanecarboxylic Acid*.—The 1-monobenzoate (2·3 g.) was heated at 100° for 1 hour with a solution of chromium trioxide (1·5 g.) in acetone (25 c.c.). After addition of a few drops of methanol to destroy excess of oxidising agent, the mixture was poured into water and extracted twice with ether. The extracts, after being washed with water, were extracted with saturated sodium hydrogen carbonate solution, and the latter then acidified and extracted twice with ether. These extracts were dried and evaporated to a solid residue (1·4 g.) which on recrystallisation from ethyl acetate gave the *benzoate* of *trans*-4-hydroxy*cyclo*hexanecarboxylic acid as long laths, m. p. 145—146° (Found: C, 67·7; H, 6·5. $C_{14}H_{16}O_4$ requires C, 67·7; H, 6·45%). This compound (2·9 g.) was saponified by being heated under reflux with 20% methanolic potassium hydroxide (10 c.c.) for 24 hours. Most of the solvent was removed, and 10% sulphuric acid was added in slight excess (Congo-red). After cooling, benzoic acid (1·32 g.), m. p. and mixed m. p. 122°, was removed, and the filtrate was evaporated to dryness. The residue, extracted continuously with ether for 6 hours, gave a solid (0·72 g.) which was dissolved in the minimum amount of boiling ethyl acetate On cooling, a small quantity (0·1 g.) of unchanged benzoate separated in prisms, m. p. 142—144°. The ethyl acetate solution was then evaporated to dryness and the residue crystallised from ether to yield *trans*-4-hydroxy*cyclo*hexanecarboxylic acid, m. p. and mixed m. p. 119—120°.

Stability of cis-4-*Hydroxy*cyclo*hexanecarboxylic Acid to Alkali*.—The *cis*-acid (0·5 g.) was refluxed with 20% methanolic potassium hydroxide (5 c.c.) for 24 hours. The solution was then concentrated, acidified with a slight excess of 2N-sulphuric acid (Congo-red), and evaporated to dryness under reduced pressure. The solid residue, extracted continuously with ether for 6 hours, furnished stout needles of the unchanged acid (0·43 g.), m. p. and mixed m. p. 152°.

Hydrogenation of trans-4-*Iodomethyl*cyclo*hexyl Benzoate*.—The compound (2·5 g.) and potassium acetate (1·1 g.) in methanol (40 c.c.) were shaken with hydrogen in the presence of Adams's platinum catalyst (0·1 g.) for 3 hours, by which time 1·01 mols. had been absorbed. The filtered solution was concentrated, diluted with water, and extracted with ether. The dried extracts on evaporation yielded a yellow oil (1·4 g.) which solidified on standing at 0°. The solid was very soluble in organic solvents but sublimed at 30—40°/10^{-4} mm. to give the *benzoate* (XXIII) of *trans*-4-methyl*cyclo*hexanol as a white powder, m. p. 34—35° (Found: C, 77·0; H, 8·4. $C_{14}H_{18}O_2$ requires C, 77·0; H, 8·3%).

trans-4-*Methyl*cyclo*hexanol* (XXIV).—The above benzoate (0·5 g.) was dissolved in dry methanol (5 c.c.) and treated with a trace of sodium methoxide (0·1 c.c. of a 20% solution in methanol). After 40 hours at room temperature, the solvent was evaporated, and the residual *trans*-4-methyl*cyclo*hexanol was identified as the phenylurethane, m. p. 123—124°, and the α-naphthylurethane, m. p. 158° (Found: C, 76·0; H, 7·5. Calc. for $C_{18}H_{21}O_2N$: C, 76·3; H, 7·5%). Skita and Faust (*loc. cit.*) give m. p. 124—125° for the *trans*-phenylurethane, and m. p. 116—117° for the *cis*; Ungnade and McLaren (*J. Amer. Chem. Soc.*, 1944, **66**, 118) give m. p. 124—124·5° for the *trans*-phenylurethane, and m. p. 156·5—157·5° for the *trans*-α-naphthylurethane.

Ethyl 4-*Methoxy*cyclo*hexanecarboxylate* (XXV).—Ethyl 4-hydroxy*cyclo*hexanecarboxylate (20 g., *cis* and *trans*) was dissolved in methyl iodide (50 g.) and refluxed during the addition, in small quantities, of silver oxide (41 g.). Dry ether (50 c.c.) was added after the addition of half the silver oxide. Finally, the mixture was refluxed for 2·5 hours. Silver compounds were then removed by filtration and thoroughly extracted with ether. Evaporation of the filtrate and washings and fractionation of the residue gave

*ethyl 4-methoxy*cyclo*hexanecarboxylate* (10·3 g.), b. p. 118—122°/16 mm., $n_D^{18°}$ 1·4541 (Found: C, 64·6; H, 9·45. $C_{10}H_{18}O_3$ requires C, 64·5; H, 9·75%). A higher-boiling fraction (6·5 g.), b. p. 140—146°/16 mm., consisted of unchanged hydroxy-ester.

*4-Hydroxymethyl*cyclo*hexyl Methyl Ether* (XXVI).—The above methoxy-ester (10 g.) dissolved in ethanol (96 c.c.) was reduced by the addition of sodium (7·5 g.), the mixture being warmed on the steam-bath. When all the sodium had reacted, water (30 c.c.) was added, and most of the alcohol distilled off. The residual solution was saturated with salt and extracted with ether to give *4-hydroxymethyl*cyclo*hexyl methyl ether* as a colourless oil (5·1 g.), b. p. 116—118°/13 mm., $n_D^{18°}$ 1·4699 (Found: C, 66·8; H, 11·4. $C_8H_{16}O_2$ requires C, 66·65; H, 11·2%). This product, a mixture of *cis*-and *trans*-forms, gave a solid α-naphthylurethane which was successively extracted with (i) cold light petroleum, (ii) boiling light petroleum (b. p. 60—80°), (iii) boiling light petroleum (b. p. 80—100°), (iv) boiling light petroleum (b. p. 100—120°). On concentration, (i) yielded fine needles, (ii) deposited a mixture of needles and dense concretions, (iii) gave a mass of dense concretions, and (iv) gave no solid. The two forms in (ii) were readily separated by flotation. Recrystallisation of the needles from light petroleum gave stellate clusters of the (cis?)-*α-naphthylurethane*, m. p. 95—96° (Found: C, 72·7; H, 7·4. $C_{18}H_{23}O_2N$ requires C, 72·8; H, 7·4%). The concretions, recrystallised from light petroleum (b. p. 60—80°), gave long prisms of the (trans?)-*α-naphthylurethane*, m. p. 113—114° (Found: C, 72·7; H, 7·4%). The m. p. of the latter compound was depressed to *ca.* 100° on admixture with the α-naphthylurethane, m. p. 117—118°, of the structurally isomeric methyl ether (XII).

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[*Received, April 5th*, 1948.]

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77. *The Configurations of α- and β-Naphthalenediazocyanides and Other Unsubstituted Hydrocarbondiazocyanides.*

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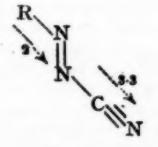
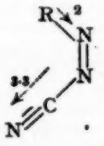
The dipole moments of the four known forms corresponding to the formula $C_{10}H_7{\cdot}N{:}N{\cdot}CN$ are explicable if the substances are *cis*- or *trans*- α- or -β-naphthalenediazocyanides. The phenyl and *p*-tolyl analogues, which are homogeneous oils at ordinary temperatures, have properties which indicate that the *trans*-configurations largely predominate. Photochemical and thermal transformations of the six substances now studied are parallel to those previously recorded for substituted benzenediazocyanides and the azobenzenes.

IN earlier work (Le Fèvre and Vine, *J.*, 1938, 431, 1878; Anderson, Le Fèvre, and Savage, *J.*, 1947, 445; Anderson, Bedwell, and Le Fèvre, *ibid.*, p. 457) studies were made of various halogeno- and nitro-derivatives of benzenediazocyanide. The measurements now to be recorded deal with *unsubstituted* hydrocarbondiazocyanides—a class for which dipole-moment data are wholly lacking.

On Hantzsch's hypothesis (for summary see "Die Diazo-verbindungen", 1921) that isomeric diazocyanides are configurationally related as *cis-trans*-cyanides it is easy to see *a priori* that the moments of the *trans*-forms (I) should exceed those of the *cis*-forms (II). The dotted

(I.) 

 (II.)

arrows indicate the component vectors found to lead to consistent analyses of Le Fèvre and Vine's results (*loc. cit.*). Hence at the outset we anticipated moment differences of 2—3 D. units.

The choice of materials for study is limited by the fact that only a few unsubstituted diazocyanides have been *separated* into two forms. The simpler monocyclic members, *e.g.*, the phenyl and the *p*-tolyl member, exist as oils at ordinary temperatures and—by analogy with molten *cis*-azobenzene (Hartley, *J.*, 1938, 633)—one should expect thermal change to proceed rapidly, giving in each case the more stable isomer. The moments and other properties now observed for these preparations are compatible with their having mainly *trans*-configurations. In the action of light they resemble *trans*-azobenzene and other pure stable diazocyanides.

All four isomeric varieties of the α- and β-naphthalene diazocyanides are solids (Danziger and Hantzsch, *Ber.*, 1897, **30**, 2545). Their moments are:

	α-Naphthalene.	β-Naphthalene.
Stable diazocyanide	5·6	6·9
Unstable diazocyanide	3·2	4·0

These data support the allocation of *cis*-configurations to the unstable, and *trans*- to the stable, forms.

It has further been found that, in the absence of light, each unstable variety in benzene solution passes spontaneously into the stable isomer. The reactions can easily be followed by changes in E and seem to be kinetically of the first order. From the velocity constants at 25° and 45°, the energy of activation, $E = \log_e(k_2/k_1)RT_1T_2/(T_2 - T_1)$, of the two inversions appears to be approximately the same, *viz.*, 23 kcals./g.-mol.:

Naphthalene-diazocyanide.	T, °K.	Half-change period, hrs.	k (hr.$^{-1}$).	E (kcals./g.-mol.).
α-	298	3·1	0·224	22·9
	318	0·26	2·568	
β-	298	4·3	0·165	23·1
	318	0·36	1·926	

This value is closer to the average reported for the analogous transformations of *cis*- into *trans*-azobenzene and its derivatives (*i.e.*, 23 kcals./g.-mol., Hartley, *loc. cit.*) than for the *p*-halogenobenzenediazocyanides (*p*-chloro-, 21·4; *p*-bromo-, 21·6, kcals./g.-mol.; Le Fèvre and Northcott, unpublished; Le Fèvre and Vine, *loc. cit.*).

In daylight the above thermal change is affected by a photochemical one. In the experimental part we record observations which demonstrate the photo-formation of *cis*- from *trans*-isomers and their reversion to the more stable forms in the dark.

The parallelism between these diazocyanides and those studied previously (*loc. cit.*), as well as with the two azobenzenes (Hartley and Le Fèvre, *J.*, 1939, 531), seems thus quite clear. Where the same type of experimental observation has been made, the appropriate arguments of Anderson, Le Fèvre, and Savage (*loc. cit.*) are applicable; *e.g.*, in particular, not only the dipole moments but also the densities and molecular refractions are consistent with Hantzsch's configurations. Were these hydrocarbondiazocyanides related as (both *trans*) cyanides and *iso*cyanides (Hodgson and Marsden, *J.*, 1944, 395), known analogies suggest that the moments should be nearly equal, while the molecular refractions should differ in the *opposite* manner to that now found. For a summary of our case for the (Hantzsch) configurational theory, see Calderbank, Le Fèvre, Northcott, and Wilson (*Chem. and Ind.*, 1948, **67**, 158, 543, 732, 782).

Experimental.

Preparation of Materials.—Benzenediazocyanide. Aniline (3·8 g.), dissolved in dilute hydrochloric acid (30 c.c., 1 : 1), was diazotised (sodium nitrite, 2·8 g. in the minimum of water) at 0°, alcohol (10 c.c.) then added, followed by ether (7 c.c.) and light petroleum (8 c.c.), and the whole cooled to −10°. The mixture was stirred to a coarse emulsion while sodium cyanide (2·5 g. in the minimum of water) was run in dropwise. The upper layer (pale yellow) was then separated as rapidly as possible, dried (Na_2SO_4), and evaporated in a vacuum. The diazocyanide (1·1 g.) remained as a yellow oil which darkened on exposure to sunlight and, if not preserved in a desiccator, decomposed in a few days to a black tar.

p-Toluenediazocyanide. This was prepared similarly from *p*-toluidine (2·2 g.), diluted hydrochloric acid (20 c.c.), sodium nitrite (1·4 g.), alcohol (10 c.c.), ether (15 c.c.), and sodium cyanide (1·2 g.). The diazocyanide (0·5 g.) was also a yellow oil, but deeper in colour than the parent substance.

α- and β-Naphthalenediazocyanides. These were similarly obtained by immediate extraction: The base (5 g.) was dissolved in alcohol (35 c.c.) and water (28 c.c.), and concentrated hydrochloric acid (10 c.c.) added, followed by sodium nitrite (3 g.) at 10°. The filtered diazo-solution, plus sodium acetate (0·25 g.) and chloroform (25 c.c.), was treated slowly and under vigorous shaking with sodium cyanide (4 g., in water, 10 c.c.). The heavy layers, after separation and drying (Na_2SO_4) gave the labile diazocyanides, as deep orange needles, on cooling to *ca.* −30° in solid carbon dioxide–alcohol. The specimens were dried in a vacuum desiccator ($CaCl_2$). The stable forms were obtained by heating a chloroform solution of the appropriate labile isomeride to 40—50° for 15 minutes and then recrystallising from the same solvent by cooling strongly.

The m. p.s observed were as follows, those recorded by Danziger and Hantzsch (*loc. cit.*) being added in parentheses:

cis-α-Naphthalenediazocyanide	57° (57—58°)	*cis*-β-Naphthalenediazocyanide	52° (51—52°)
trans-α-Naphthalenediazocyanide	117·5° (116°)	*trans*-β-Naphthalenediazocyanide	132·5° (131°)

During each of the six preparations above, from the addition of aqueous cyanide onwards, all operations were conducted in the absence of light.

Apparatus and Technique.—Various quartz oscillator circuits, all essentially of the types previously described (*J.*, 1948, 1949), have been used. One of these, constructed for the observations at 45°, where only readings of capacity change with time were required, had a variable radio-condenser (0·0005 μ F.) and a small micrometer condenser (2—8 μμF. range, copied from Groves, *J.*, 1938, 1144), mounted and connected in parallel under the chassis. The desired readings were conveniently taken on the protruding micrometer head. During the course of the work, glass cells (see Le Fèvre, "Dipole Moments", Methuen, 1935, p. 32) were replaced by concentric brass tubular condensers, and liquid paraffin, dyed a deep red (with Waxoline Red E.P.S.), adopted as a thermostat liquid instead of water.

The brass tubes were mounted in a glass envelope after the manner illustrated by Higasi (*Sci. Papers Inst. Phys. Chem. Res. Tokyo*, 1934, **24**, 57) except that we deliberately made the length/diameter ratio larger (*ca.* 10 : 1). These alterations have proved especially advantageous during prolonged "rate" determinations, which were formerly liable to spoliation by the slow deterioration of the silver layers. In other respects we have followed routine practice (Le Fèvre, *op. cit.*, p. 35; *J.*, 1937, 1805).

Dielectric-polarisation Data.—These are tabulated below together with indications of the conditions under which they were obtained. The symbols used denote the following quantities: w weight fraction, ϵ dielectric constant ($\lambda = 300$ m.), d_4° density, and p specific polarisation. Subscripts 1 and 2 refer to solute and solvent, respectively. $_{\infty}P_T$ indicates the total polarisation of a solute at infinite dilution. The extrapolation is made by calculation, assuming that the densities and dielectric constants of a series of solutions have rectilinear dependence on the concentration, *i.e.*, $d_{12} = d_2(1 + \beta w_1)$ and $\epsilon_{12} = \epsilon_2(1 + \alpha w_1)$. The approximate constancy of the quantities $\alpha\epsilon_2$ and βd_2 justifies this treatment in the present instances. The specific polarisations at infinite dilution are obtained as $p_2(1 - \beta) + C\alpha\epsilon_2$, where $p_2 = (\epsilon_2 - 1)/(\epsilon_2 + 2)d_2$ and $C = 3/d_2(\epsilon_2 + 2)^2$; $_{\infty}P_T$ is given by $M_1 \times (p_1)_{w_1=0}$. Benzene is used as solvent throughout. The values of C and p_2 are:

Temp.	25°.	27°.	30°.
C	0·1881	0·1890	0·1901
p_2	0·3409	0·3413	0·3416

Benzenediazocyanide.

$100w_1$.	$\epsilon^{25°}$.	$d_4^{25°}$.	$\alpha\epsilon_2$.	β.	$100\omega_1$.	$\epsilon^{25°}$.	$d_4^{25°}$.	$\alpha\epsilon_2$.	β.
0	2·2725	0·87378	—	—	—	—	—	—	—
(A) Freshly prepared specimens dissolved soon after isolation, under ordinary laboratory daylight:									
0·5859	2·3976	0·87507	21·35	0·252	1·1829	2·5251	0·87643	21·35	0·256
(B) Above solutions exposed to sunlight in clear glass flasks for about 0·5 hour and immediately remeasured:									
0·5859	2·3682	—	16·33	—	1·1829	2·4733	—	17·00	(0·26)
(C) Solutions from (B) then stored in the dark in amber glass bottles and remeasured after 4 hours with the greatest possible exclusion of light:									
0·5859	2·3974	—	21·31	—	1·1829	2·5250	—	21·43	(0·26)

p-*Toluenediazocyanide.*

The same sequence of experiments was followed as above (bath temp. 25°).

(A)	0·7859	2·3700	0·87580	12·4	0·294	0·9107	2·3745	0·87621	11·2	0·305
	0·9076	2·4113	0·87613	15·3	0·297					
(B)	0·7859	2·3574	—	10·8	—	0·9107	2·3705	—	10·8	(0·3)
	0·9076	2·3619	—	9·9	—					
(C)	After 10 hours in the dark:									
	0·7859	2·3928	—	15·3	—	0·9107	2·4114	—	15·25	(0·3)
	0·9076	2·4113	—	15·3	—					

α-*Naphthalenediazocyanides.*

(A) Solutions of the pure labile form made up in brown glass bottles and handled with the maximum exclusion of light (bath temp. 27°).

$100\omega_1$.	$\epsilon^{27°}$.	$d_4^{27°}$.	$\alpha\epsilon_2$.	β.	$100\omega_1$.	$\epsilon^{27°}$.	$d_4^{27°}$.	$\alpha\epsilon_2$.	β.
0	2·2685	0·87130	—	—	0·7386	2·3187	—	6·80	—
0·4893	2·3015	0·87258	6·74	0·301	0·7912	2·3222	0·87338	6·78	0·302
0·5062	2·3029	0·87267	6·80	0·310					

(B) As in (A) but with the stable form:

0·4928	2·3638	0·87254	19·34	0·289	0·8027	2·4242	0·87331	19·40	0·287
0·6892	2·4015	0·87301	19·30	0·285	1·0252	2·4668	0·87386	19·34	0·285

(C) As in (B) but at 30°:

0	2·2628	0·86848	—	—	1·1630	2·4873	0·87139	19·3	0·289
0·6507	2·3897	0·87007	19·5	0·288					

(D) Solutions of $100w_1 = 0·8027$ and 1·0252 from series (B), above, were remeasured after exposure to sunlight in clear glass flasks for 0·5 hour, and then again after being stored in the dark for two days:

$100w_1$.	$\epsilon_{\text{initial}}$.	$\alpha\epsilon_2$.	$\epsilon_{\text{exposed}}$.	$\alpha\epsilon_2$.	ϵ_{final}.	$\alpha\epsilon_2$.
0·8027	2·4242	19·4	2·3907	15·2	2·4232	19·3
1·0252	2·4668	19·3	2·4179	14·6	2·4658	19·2

β-Naphthalenediazocyanides.

(A) As for the α-compound (A), except that bath temperature was 25° :

$100w_1$.	$\epsilon^{25°}$.	$d_4^{25°}$.	$\alpha\epsilon_2$.	β.	$100w_1$.	$\epsilon^{25°}$.	$d_4^{25°}$.	$\alpha\epsilon_2$.	β.
0	0·2725	0·87378	—	—	0·2148	2·2946	0·87448	10·29	0·373
0·1116	2·2843	0·87417	10·60	0·400	0·3853	2·3240	0·87506	—	0·380
0·1947	2·2930	0·87446	10·52	0·400					

(B) As for the α-compound (B), but at 25° :

0·2490	2·3447	0·87454	29·0	0·349	0·4821	2·4129	0·87529	29·8	0·358
0·2635	2·3583	0·87459	29·0	0·358	0·4855	2·4162	0·87526	29·6	0·348
0·3795	2·3859	0·87495	29·9	0·352	0·7569	2·5013	0·87616	—	0·360

Molecular Refractions of the Isomeric Naphthalenediazocyanides.—These were determined in chlorobenzene solutions at concentrations of 1—2%, with an Abbé refractometer (temp., 25°).

$100w_1$.	$d_4^{25°}$.	$n_D^{25°}$.	r_{12} (c.c.).	$[R_L]_D$ (c.c.).	$100w_1$.	$d_4^{25°}$.	$n_D^{25°}$.	r_{12} (c.c.).	$[R_L]_D$ (c.c.).
0	1·1015	1·5252	0·36203	—	—	—	—	—	—
α-Naphthalenediazocyanide (stable form)					*α-Naphthalenediazocyanide (labile form)*				
1·7512	1·1081	1·5294	0·36193	64·5	1·8789	1·1091	1·5290	0·36166	62·0
β-Naphthalenediazocyanide (stable form)					*β-Naphthalenediazocyanide (labile form)*				
2·0694	1·1107	1·5312	0·36195	64·9	1·9481	1·11075	1·5310	0·36173	62·8

The molecular refractions for the benzene- and toluene-diazocyanides have been calculated from previous determinations on *p*-bromobenzenediazocyanide (52·8 c.c.; Le Fèvre and Vine, *loc. cit.*) by deducting 8·9 c.c. for Br and adding 1·1 or 5·7 for H or CH_3, respectively.

Apparent Dipole Moments from Above Data.—These are given in the last column of the following table.

Diazocyanide.	Ref. to tables.	Mean $\alpha\epsilon_2$.	Mean β.	M.	$_\infty P_T$.	$[R_L]_D$.	μ, D.
Benzene-	A	21·35	0·254	131·1	560	45	5·0
,, ...	B	16·7	(0·26) *	,,	445	,,	4·4
,, ...	C	21·37	(0·26) *	,,	560	,,	5·0
p-Toluene-	A	*ca.* 13	0·299	145·1	389	50	4·05
,, ...	B	10·5	(0·3) *	,,	321	,,	3·6
,, ...	C	15·3	(0·3) *	,,	452	,,	4·4
α-Naphthalene-	A	6·78	0·304	181·1	275	62·0	3·2
,, ...	B	19·35	0·287	,,	706	64·5	5·6
,, ...	C	19·4	0·288	,,	712	64·5	5·6
β-Naphthalene-	A	10·47	0·388	,,	394	62·8	4·0
,, ...	B	29·46	0·354	,,	1043	65·0	6·9

* Maximum estimates.

Discussion.—The significant points demonstrated by the above figures are that, when dissolved in benzene: (*a*) benzenediazocyanide is probably a single form with a *trans*-configuration, since its observed moment (5·0 D.) falls to 4·4 D. on sunlight illumination, but is restored after a few hours when this is terminated; (*b*) *p*-toluenediazocyanide as prepared contains some *cis*-isomer, since its moment (4·05 D.) falls to 3·6 D. in daylight, and rises again to 4·4 D. on standing in the dark (4·4 D. is presumably the moment of the *trans*-form); (*c*) the moments of the pairs of α- (3·2 and 5·6 D.) and β- (4·0 and 6·9 D.) naphthalenediazocyanides differ by 2—3 D., as expected, the higher value in each case belonging to the *trans*-isomer; and (*d*) *trans*-α-naphthalenediazocyanide by irradiation (sunlight) acquires an apparent moment of 4·9 D., corresponding to a *cis*-content of approximately 35% (evaluated by applying a mixture law to μ^2_{cis} and μ^2_{trans}), which reverts to 5·6 D. (100% *trans*) in the absence of light. The opposing effects of the photochemical (*trans* ⟶ *cis*) and the dark thermal (*cis* ⟶ *trans*) reactions are thus qualitatively demonstrated. For comparison it may be noted that benzene solutions of *p*-bromobenzenediazocyanide and azobenzene have been found to contain 20% and 22% respectively of the *cis*-forms at equilibrium in sunlight (Le Fèvre and Vine; Hartley; *locc. cit.*; Hartley and Le Fèvre, *J.*, 1939, 531). Section (A) of *p*-toluenediazocyanide suggests that the undiluted cyanide undergoes photo-inversion more readily than its benzene analogue, since the order in which the three solutions are made up seems to determine the magnitude of $\alpha\epsilon_2$, those

prepared first from a given batch having the highest values and *vice versa*. After irradiation, etc., these differences disappear (sections B and C).

This investigation has been assisted by grants from the Commonwealth Research Fund and has utilised apparatus originally provided by this Society. Grateful acknowledgment is now made.

UNIVERSITY OF SYDNEY, N.S.W., AUSTRALIA. [*Received, April 15th*, 1948.]

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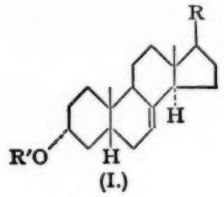
78. *The Application of the Method of Molecular Rotation Differences to Steroids. Part IX. Concerning* u-*Ergostadienol.*

By D. H. R. BARTON and E. MILLER.

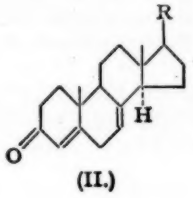
Partial catalytic hydrogenation of ergosterone in neutral solution affords a complex mixture of products from which *coproergosta*-7(8) : 22(23)-*diene*, ergosta-7(8) : 22(23)-dien-3-one, ergosta-7(8) : 22(23)-dien-3(β)-ol, and coproergosta-7(8) : 22(23)-dien-3(α)-ol have been isolated. The properties of coproergosta-7(8) : 22(23)-dien-3(α)-ol and its derivatives are identical with those recorded for *u*-ergostadienol, thus confirming the structure previously suggested for the latter.

Complete catalytic hydrogenation of *iso*ergosterone in neutral solution gives, after removal of unsaturated material, a mixture of ergostan-3(β)-ol and coproergostan-3(α)-ol.

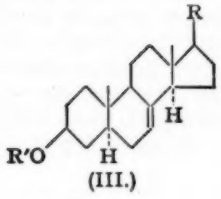
IN Part III of this series (*J.*, 1946, 1116) the formula (I; R = C_9H_{17}, R′ = H) was suggested for *u*-ergostadienol, principally from considerations of the optical rotatory powers of this substance and its derivatives (see Windaus and Auhagen, *Annalen*, 1929, **472**, 185). If this



(I.)

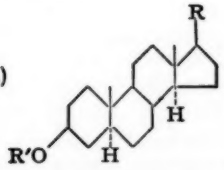


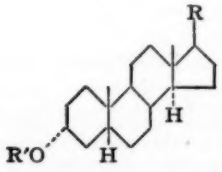
(II.)



(III.)

(IV.)

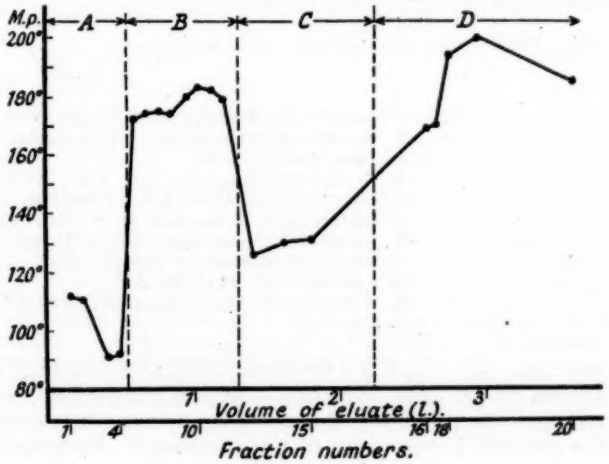




(V.)

view were correct it would be expected that partial catalytic hydrogenation of ergosterone (II; R = C_9H_{17}) in neutral solution would afford, amongst other products, ergosta-7(8) : 22(23)-dien-3(β)-ol (α-dihydroergosterol) (III; R = C_9H_{17}, R′ = H) and coproergosta-7(8) : 22(23)-

Fraction No.	*Elutriant.*
1—4	50 *Petrol* : 50 *benzene* (*A*)
5—12	50 *Petrol* : 50 *benzene* (*B*)
13—15	50 *Petrol* : 50 *benzene* (*C*)
16	66 *Benzene* : 34 *ether* (*D*)
17—19	*Ether* (*D*)
20	66 *Ether* : 34 *chloroform* (*D*)



dien-3(α)-ol (*u*-ergostadienol) by analogy with the behaviour of cholest-4(5)-en-3-one, which gives cholestan-3(β)-ol (IV; R = C_8H_{17}, R′ = H) and coprostan-3(α)-ol (V; R = C_8H_{17}, R′ = H) under similar conditions. In agreement with expectation we have found that catalytic hydrogenation of ergosterone in chloroform solution until 1·1 molar proportions of hydrogen have been absorbed gives a complex mixture of products which can be resolved by chromatography as illustrated in the diagram. The more easily eluted fractions (A) furnished on rechromatography a homogeneous hydrocarbon, $C_{28}H_{46}$, the constitution of which is discussed later. Fractions (B) on repeated recrystallisation, afforded ergosta-7(8) : 22(23)-dien-3-one (α-ergostadienone) (VI; R = C_8H_{17}), whilst fractions (C) gave unchanged ergosterone. Fractions (D) were combined and separated by digitonin treatment. By

TABLE I.

	Coproergosta-7(8) : 22(23)-dien-3(α)-ol.		*u*-Ergostadienol.		
Derivative.	M. p.	$[\alpha]_D$ in $CHCl_3$.	M. p.	$[\alpha]_D$ in $CHCl_3$.	Refs.
Alcohol.....	170·5°	+43°	170°	+42°	1
Acetate	130	+59	128	+58	1
Benzoate	159	+51	159	—	2

1. Windaus and Auhagen, *Annalen*, 1929, **472**, 185.
2. Laucht, *Z. physiol. Chem.*, 1937, **246**, 171.

resolution of the insoluble digitonide, α-dihydroergosterol (III; R = C_8H_{17}, R′ = H) was obtained, whilst from the non-digitonide-forming fraction coproergosta-7(8) : 22(23)-dien-3(α)-ol was isolated. The properties of the latter and its derivatives are summarised in Table I and compared with those recorded in the literature for *u*-ergostadienol and its derivatives. The agreement between the sets of figures, combined with the evidence previously adduced, is sufficient to establish beyond doubt the correctness of the view we have advocated as to the identity of these substances.

The hydrocarbon, $C_{28}H_{46}$, obtained from the more easily eluted fractions of the chromatogram must contain two ethylenic linkages. The possible formulæ for this substance, which has m. p. 122·5°, $[\alpha]_D$ +34° (in chloroform), are (VII; R = C_8H_{17}), (VIII; R = C_8H_{17}),

TABLE II.

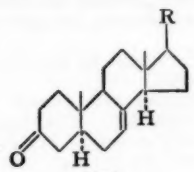
		$[M]_D$,			
Substance.	Solvent.	3(α)-ol.	3-H.	Δ.	Refs.
Coprostan-3(α)-ol	$CHCl_3$	+124°	+ 97°	−27°	1, 2, 3
Coproergostan-3(α)-ol	$CHCl_3$	+101	+ 77	−24	4, 5
3(α)-Hydroxycholanic acid methyl ester	Me_2CO	+129	+ 94	−35	6, 7
3(α)-Hydroxychol-11(12)-enic acid methyl ester	MeOH	+163	+127 *	−36	7, 8
3(α)-Hydroxy-11(α) : 12(α)-oxidocholanic acid methyl ester	Me_2CO	+145	+113	−32	7, 8
3(α)-Hydroxy-12-ketoætiocholanic acid methyl ester	$CHCl_3$	+501	+473	−28	9, 10
Average	—	—	—	−30	—
Coproergosta-7(8) : 22(23)-dien-3(α)-ol	$CHCl_3$	+171	+129	−42	11
Anomalous.					
3(α) : 7(α)-Dihydroxyætiocholanic acid methyl ester	$CHCl_3$	+ 7	+104	+97	9

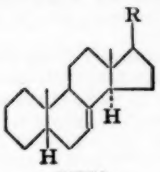
* In Me_2CO.

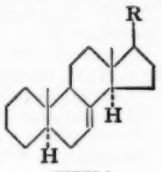
1. Isiguro and Watanabe, *J. Pharm. Soc. Japan*, 1938, **58**, 260.
2. Stavely and Bergmann, *J. Org. Chem.*, 1937, **1**, 572.
3. *Idem, ibid.*, p. 575.
4. Wetter and Dimroth, *Ber.*, 1937, **70**, 1665.
5. Laucht, *Z. physiol. Chem.*, 1937, **246**, 171.
6. Seebeck and Reichstein, *Helv. Chim. Acta.*, 1943, **26**, 536.
7. Alther and Reichstein, *ibid.*, 1942, **25**, 805.
8. Press and Reichstein, *ibid.*, p. 878.
9. Lardon, *ibid.*, 1947, **30**, 597.
10. Wenner and Reichstein, *ibid.*, 1944, **27**, 965.
11. Exptl.

and (IX; R C_8H_{19}). Of these (VIII; R = C_8H_{17}) is that already allotted to α-ergostadiene, m. p. 124—125°, $[\alpha]_D$ −10° (in chloroform) (Heilbron *et al.*, *J.*, 1932, 1705), and although the rotation should probably be somewhat more negative there is no reason to doubt the essential homogeneity of this compound. Formula (IX; R = C_8H_{19}) is unlikely because

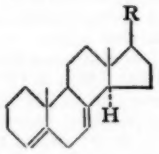
all the other substances isolated possessed an ethylenic linkage at the 22 : 23-position. Formula (VII; R = C_9H_{17}), on the other hand, would be related in molecular rotation to coproergosta-7(8) : 22(23)-dien-3(α)-ol in the manner indicated in Table II. The agreement between the Δ value calculated assuming this relationship and the Δ values found for comparable substances

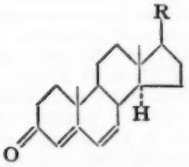

(VI.)


(VII.)


(VIII.)

(IX.)




(X.)

of known structure (see Table II) is support for our view that the unknown hydrocarbon is *coproergosta*-7(8) : 22(23)-*diene* (VII; R = C_9H_{17}). It should be pointed out that the comparison of molecular rotations made here is not invalidated by the possibility of " vicinal action " as will be seen from a consideration of our earlier study of this subject (*J.*, 1948, 783). Further proof for the correctness of the formula (VII; R = C_9H_{17}) was obtained by the catalytic hydrogenation of the diene in neutral solution. This gave a hydrocarbon, $C_{28}H_{48}$, m. p. 107°, $[\alpha]_D$ +48° (in chloroform), whose molecular rotation difference with respect to its progenitor was +55° and corresponded therefore to the average value of +61° (see Part II; *J.*, 1946, 512) required for the reduction of the 22(23)-ethylenic linkage in the sterol side chain. In consequence this reduction product is formulated as *coproergost*-7(8)-*ene* (VII; R = C_9H_{19}).

One of the former objections to the formulation of *u*-ergostadienol as coproergosta-7(8) : 22(23)-dien-3(α)-ol was the fact that *u*-ergostanol, the fully saturated derivative of *u*-ergostadienol, did not correspond to the fully saturated alcohol obtained by Wetter and Dimroth (*Ber.*, 1937, **70**, 1665) by hydrogenation of ergosterone under drastic conditions, and which was tentatively formulated by them as coproergostan-3(α)-ol (V; R = C_9H_{19}, R′ = H) (compare Part III, *loc. cit.*). We have provided confirmation for this formula of Wetter and Dimroth by a study of the hydrogenation of *iso*ergosterone (X; R = C_9H_{17}) in neutral solution. After removal of unsaturated material from the reaction product and resolution with digitonin ergostan-3(β)-ol (IV; R = C_9H_{19}, R′ = H) and coproergostan-3(α)-ol (V; R = C_9H_{19}, R′ = H) were obtained, the latter agreeing in all respects with the alcohol of Wetter and Dimroth. Since we have fully established the identity of *u*-ergostadienol and coproergosta-7(8) : 22(23)-dien-3(α)-ol it follows that our views (Part III, *loc. cit.*) as to the inhomogeneity of *u*-ergostanol now receive confirmation.

Experimental.

(M. p.s are uncorrected.)

The substances whose rotations are listed below were dried in a vacuum at 20° below their m. p.s, or at 120°, whichever was the lower temperature. All rotations are for the Na_D line and in chloroform solution. They were taken in 1 dm. macro- or micro-tubes, the use of the latter being specifically indicated after each recorded measurement.

Standard chemical operations were carried out as in Part IV (*J.*, 1948, 783) unless specified to the contrary.

Partial Hydrogenation of Ergosterone in Neutral Solution.—10 G. of ergosterone (prepared by Oppenauer oxidation of ergosterol), dissolved in 150 ml. of chloroform, were shaken with 500 mg. of reduced platinum oxide catalyst in an atmosphere of hydrogen until the volume of gas absorbed corresponded to 1·1 molar proportions. The catalyst was removed by filtration and the solvent by evaporation under reduced pressure. The residue was dissolved in the minimum of light petroleum (b. p. 40—60°) and chromatographed over a column of Birlec alumina, 40 cm. long and 3 cm. in diameter. The resulting chromatogram, shown in the diagram, was treated as outlined below.

Fractions (A) were combined and rechromatographed over the same quantity of alumina. Elution with light petroleum furnished, after crystallisation from ethyl acetate, long needles of *coproergosta*-7(8) : 22(23)-*diene*, m. p. 122·5°, $[\alpha]_D$ +34° (*c*, 2·04; micro-tube), $[M]_D$ +129° (Found : C, 87·7; H, 12·0. $C_{28}H_{46}$ requires C, 88·0; H, 12·0%).

Catalytic hydrogenation of coproergosta-7(8) : 22(23)-diene in ethyl acetate solution using a platinum oxide catalyst until there was no further absorption of hydrogen gave, after recrystallisation from ethyl acetate–methanol, *coproergost*-7(8)-*ene*, m. p. 107°, $[\alpha]_D$ +48° (*c*, 1·84; micro-tube), $[M]_D$ +184° (Found : C, 87·5; H, 12·1. $C_{28}H_{48}$ requires C, 87·5; H, 12·5%). The hydrocarbon gave a strong colour when tested for unsaturation with tetranitromethane.

Fractions B were combined and repeatedly recrystallised from ethyl acetate–methanol to give ergosta-7(8) : 22(23)-dien-3-one (α-ergostadienone), m. p. 184—185°, undepressed by admixture with an authentic specimen (Part V, *J.*, 1948, 1354).

Fractions C were combined and recrystallised from ethyl acetate–methanol to furnish unchanged ergosterone, m. p. 131°, undepressed on admixture with the starting material.

Fractions D were combined, dissolved in 95% ethyl alcohol and treated with excess of digitonin dissolved in the same solvent (Schönheimer, *Z. physiol. Chem.*, 1933, **215**, 59). The digitonide that separated was decomposed by pyridine and the digitonin precipitated with excess of dry ether. After removing the digitonin by filtration the solution was evaporated under reduced pressure and the residue recrystallised from ethyl acetate–methanol to give ergosta-7(8) : 22(23)-dien-3(β)-ol (α-dihydroergosterol), m. p. 175°, undepressed on admixture with an authentic specimen (Part V, *loc. cit.*).

The alcoholic mother liquors remaining from the separation of the above mentioned digitonide were evaporated under reduced pressure and the residue extracted with dry ether. Evaporation of the filtered ethereal solution afforded, after crystallisation from ethyl acetate–methanol, coproergosta-7(8) : 22(23)-dien-3(α)-ol, m. p. 170·5°, $[\alpha]_D$ +43° (*c*, 2·32), +44° (*c*, 0·80), $[M]_D$ +171°. Acetylation of this alcohol gave the acetate, recrystallised from ethyl acetate–methanol, m. p. 130°, $[\alpha]_D$ +59° (*c*, 4·77; micro-tube), $[M]_D$ +260°, whilst benzoylation furnished the corresponding benzoate, recrystallised from ethyl acetate, m. p. 159°, $[\alpha]_D$ +50° (*c*, 4·65; micro-tube), +51° (*c*, 2·70; micro-tube), $[M]_D$ +256°. Coproergosta-7(8) : 22(23)-dien-3(α)-ol and its derivatives gave negative Tortelli–Jaffé tests, thus confirming the absence of contaminants having a 7(8)-ethylenic linkage and the ergostane configuration at C_5.

Hydrogenation of iso*Ergosterone in Neutral Solution.*—2·8 G. of *iso*ergosterone, prepared by isomerisation of ergosterone in chloroform solution with dry hydrogen chloride, were dissolved in 75 ml. of ethyl acetate, 100 mg. of platinum catalyst were added, and the resulting solution shaken in an atmosphere of hydrogen for 36 hours until there was no further absorption. The catalyst was removed by filtration and the solvent by evaporation under reduced pressure. The residue was taken up in carbon tetrachloride and subjected to the Anderson–Nabenhauer procedure (*J. Amer. Chem. Soc.*, 1924, **46**, 1957) for the removal of unsaturated material. The crystalline product from this treatment was dissolved in 95% ethyl alcohol and excess of digitonin in the same solvent was added (Schönheimer, *loc. cit.*). The precipitated digitonide was resolved in the same way as is detailed above and furnished ergostan-3(β)-ol, m. p. 143—144°, undepressed on admixture with an authentic specimen (Part V, *loc. cit.*). The mother liquors from filtration of the insoluble digitonide were worked up in a similar manner to that detailed above to give coproergostan-3(α)-ol, m. p. 139°. By acetylation coproergostan-3(α)-yl acetate, recrystallised from methanol, m. p. 99°, $[\alpha]_D$ +39° (*c*, 3·07; micro-tube), +38° (*c*, 2·57; micro-tube), $[M]_D$ +173°, was obtained. Wetter and Dimroth (*Ber.*, 1937, **70**, 1665) give m. p. 139—140°, $[\alpha]_D$ +25° (in chloroform), $[M]_D$ +101°, for their coproergostan-3(α)-ol and m. p. 99° for the corresponding acetate. The difference in molecular rotation (Δ_1 value) for Wetter and Dimroth's alcohol compared with the acetate obtained here is +72° which is in satisfactory agreement with the average value for this constant given in Part III (*J.*, 1946, 1116). For *u*-ergostanyl acetate which, as we have argued, should be identical with coproergostan-3(α)-yl acetate, Windaus and Auhagen (*Annalen*, 1929, **472**, 185) give m. p. 96°, $[\alpha]_D$ +39° (in chloroform), whilst Dithmar and Achtermann (*Z. physiol. Chem.*, 1932, **205**, 55) record m. p. 97°, $[\alpha]_D$ +41° (in chloroform).

This work was carried out during the tenure of an I.C.I. Fellowship by one of us (D. H. R. B.). We are indebted to the Chemical Society for a grant.

IMPERIAL COLLEGE OF SCIENCE AND TECHNOLOGY,
LONDON, S.W.7.

[*Received, April 28th*, 1948.]

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79. *The Friedel–Crafts Reaction on Fluoranthene.*

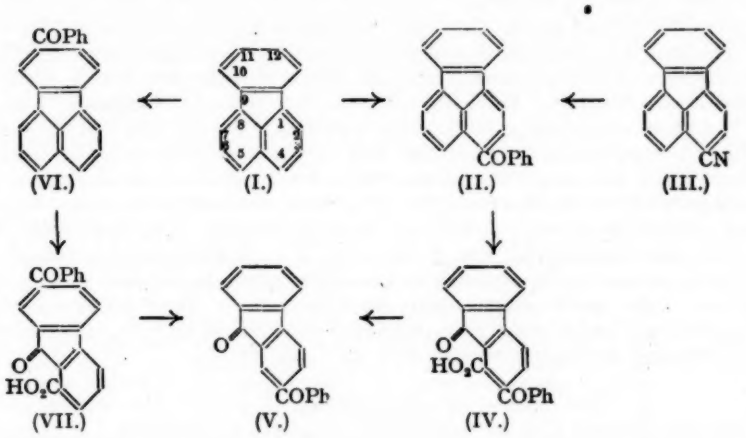
By NEIL CAMPBELL and W. W. EASTON.

The products of the Friedel–Crafts reaction on fluoranthene have been isolated by chromatographic separation. The results differ in some cases from those of previous workers. Benzoylation and phthaloylation give approximately equal quantities of the 4- and 11-isomers; acetylation, 4-, 11(?)-, and a diacetylfluoranthene; oxalyl chloride, fluoranthene-11-carboxylic acid and a dicarboxylic acid with the carboxyl groups probably in the 4 : 11- or 4 : 12-positions. The 11-acid is also formed by the Houben–Fischer method. 1 : 2 : 3 : 4-Tetrahydrofluoranthene and benzoyl chloride give 5-benzoyl-1 : 2 : 3 : 4-tetrahydrofluoranthene, while the benzoylation of naphthalene in nitrobenzene gives approximately equal quantities of 1- and 2-benzoylnaphthalenes.

VON BRAUN and MANZ (*Annalen*, 1932, **496**, 170), the only workers to investigate thoroughly the Friedel–Crafts reaction on fluoranthene, stated that the main products were 11-substituted derivatives. Since, however, separation of the isomers was difficult, too much reliance cannot be placed on these semi-quantitative results nor is the purity of the products always above

suspicion. It was, therefore, decided to repeat and expand von Braun's work, using the chromatographic technique to separate and purify the products. Our results confirm the necessity of these precautions.

The benzoylation of fluoranthene (I) with benzoyl chloride and aluminium chloride by either the Perrier method (*Bull. Soc. chim.*, 1904, **31**, 859) or the usual procedure gave a little unchanged fluoranthene and a mixture of 4- and 11-benzoylfluoranthenes, the quantitative separation of which was not effected. Nevertheless the results show that, contrary to the statement of von Braun and Manz (*loc. cit.*), 4-benzoylfluoranthene (II) is not a mere by-product, and indicate that it is formed in approximately equal quantities with the 11-isomer. The constitution of the 4-benzoylfluoranthene was established by showing it to be identical with a sample prepared from 4-cyanofluoranthene (III) (von Braun and Manz, *Annalen*, 1931, **488**, 111). On oxidation it yielded 1-*carboxy*-2-*benzoylfluorenone* (IV), m. p. 227—228°, which on decarboxylation gave 2-benzoylfluorenone (V).



The isomeric benzoylfluoranthene proved to be 11-benzoylfluoranthene (VI) since on oxidation it gave 7-*benzoylfluorenone*-1-*carboxylic acid* (VII), m. p. 206—209°, whose structure follows from the facts that while the acid is different from the above isomer it yields 2-benzoylfluorenone on decarboxylation. A feature of the 11-benzoyl compound is the ease with which it forms a dinitrophenylhydrazone in contrast to the 4-isomer. This is probably a steric effect, since it was found that 1-benzoylnaphthalene forms a dinitrophenylhydrazone by Allen's method (*J. Amer. Chem. Soc.*, 1930, **52**, 2955) only on boiling for some time, while the 2-benzoylnaphthalene reacts rapidly. Other benzoyl-hydrocarbons such as 2-benzoylfluorene also react rapidly with dinitrophenylhydrazine.

Buu-Hoï and Cagniant (*Rec. Trav. chim.*, 1943, **62**, 719) claim to have prepared pure 11-acetylfluoranthene, m. p. 68°, in good yield by the Friedel–Crafts reaction, but the difficulties obviously encountered hardly support their statement. They orientated the compound by submitting the oxime to the Beckmann transformation. The product, m. p. 190°, is stated to be identical with 11-acetamidofluoranthene (von Braun and Manz, *Annalen*, 1931, *loc. cit.*), but no mixed m. p. with an authentic sample is cited and it is noteworthy that this compound has not yet been analysed. Repetition of the work of Buu-Hoï and Cagniant has confirmed our suspicions that these workers obtained only a highly impure product. By following their instructions closely and submitting the crude product to chromatographic purification we found that it contains about 60% of fluoranthene; 4-*acetylfluoranthene*, m. p. 131—132°, identical with a sample prepared from 4-cyanofluoranthene; an isomer, possibly 11-*acetylfluoranthene*, m. p. 101—102°; and a *diacetylfluoranthene*, m. p. 140—142°. The oximes of the two acetylfluoranthenes had higher m. p.s than those quoted by Buu-Hoï and Cagniant.

In view of the above the 11'-fluoranthyl-2-cinchonic acid and 11'-fluoranthyl-2-quinoline prepared by these authors may well be the corresponding 4'-fluoranthyl compounds.

Von Braun and Manz (*Annalen*, 1932, *loc. cit.*) by the phthaloylation of fluoranthene obtained 4- and 11-benzoylfluoranthene-2'-carboxylic acids and we have confirmed the structures assigned by them by decarboxylation to the corresponding benzoylfluoranthenes. The same authors (*Annalen*, 1932, *loc. cit.*) by the action of oxalyl chloride and aluminium chloride on fluoranthene

obtained a mono- and a di-carboxylic acid in the ratio 2 : 1 together with a very small quantity of a second carboxylic acid, the main acid being shown to be fluoranthene-11-carboxylic acid and the other the 4-acid. Repetition of this work gave substantially the same results, but we were unable to isolate any 4-acid.

Fluoranthene-4-carboxylic acid was readily decarboxylated with copper in boiling quinoline, whereas the 11-acid was unaffected under these conditions. The fact that the dicarboxylic acid was decarboxylated to fluoranthene-11-carboxylic acid thus affords good evidence that it is the 4 : 11- or the 4 : 12-dicarboxylic acid.

Carboxylation of fluoranthene by the Houben method (Houben and Fischer, *Ber.*, 1931, **64**, 240, 2636) yielded a mixture from which we were able to isolate in the pure state only fluoranthene-11-carboxylic acid in 35% yield.

The 4-substituted fluoranthenes crystallise in deep yellow needles while the 11-isomers are colourless (or nearly so) plates with a blue fluorescence. The 4-isomers have higher m. p.s and are less strongly adsorbed on alumina.

The nature of the solvent greatly influences substitution of naphthalene by the Friedel–Crafts reaction, acetylation, for example, in carbon disulphide giving approximately 60% of 1-acetylnaphthalene (Chopin, *Bull. Soc. chim.*, 1924, **35**, 610; St. Pfau and Ofner, *Helv. Chim. Acta*, 1926, **9**, 669; Lock, *Monatsh.*, 1943, **74**, 77; cf. Buu-Hoï and Cagniant, *Bull. Soc. chim.*, 1945, **12**, 307) and in nitrobenzene 90% of the 2-isomer. We investigated the benzoylation of naphthalene in nitrobenzene in the hope that 2-benzoylnaphthalene would be the main product and consequently that 3-benzoylfluoranthene might be obtained by the analogous method. So far as we could judge, however, the two benzoylnaphthalenes resulted in almost equal quantities.

The main product from the reaction of benzoyl chloride and aluminium chloride with 1 : 2 : 3 : 4-tetrahydrofluoranthene was *5-benzoyl*-1 : 2 : 3 : 4-*tetrahydrofluoranthene* with much smaller quantities of an isomer isolated as the dinitrophenylhydrazone and a *dibenzoyltetrahydrofluoranthene*. The result was contrary to expectations, since under similar conditions, tetrahydronaphthalene yields mainly 6-substituted products (Schwarin, *Ber.*, 1902, **35**, 2511; v. Braun, Kirschbaum, and Schuhemann, *Ber.*, 1920, **53**, 1155).

Experimental.

Unless otherwise stated the methods of preparation and the properties of the compounds used are those given in the literature. The identity of substances was established by mixed m. p.s with authentic samples, and the purity of products determined by the sharpness of their m. p.s determined on a Kofler micro-m. p. apparatus (*Mikrochem.*, 1934, **15**, 242). Chromatographic adsorptions (for fuller details see Easton, Thesis, Edinburgh, 1947) were carried out with alumina (Brockmann) as adsorbent, and analyses were done by Drs. Weiler and Strauss, Oxford. All fluorescence observations were made under a Hanovia ultra-violet lamp.

Benzoylation of Fluoranthene.—(*a*) Aluminium chloride (17·5 g.) was slowly added with shaking to benzoyl chloride (17·5 g.), and the mixture heated gently and then cooled. Carbon disulphide (100 c.c.) was added, and the mixture heated on the water-bath, and then cooled slightly. Fluoranthene (25 g.) was added during ½ hour, and the slurry heated on the water-bath for another 10 minutes, then cooled thoroughly, and filtered. The solid, after being stirred into water (400 c.c.) and concentrated hydrochloric acid (25 c.c.) and boiled for 15 minutes, yielded a dark brown oil which was extracted with ether (1000 c.c.). The extract, after being washed with sodium carbonate solution and dried ($CaCl_2$), yielded on distillation yellow crystals (25 g.), m. p. 78—105°.

The crude solid (5 g.) was dissolved in a 4 : 1 mixture of light petroleum (b. p. 80—100°) and benzene, and chromatographed on a column of alumina 28″ × 0·86″, and developed with the same mixture. A blue fluorescent eluate was first obtained which yielded fluoranthene (0·4 g.), m. p. 109—110°. On the column was left a lower band with a dull yellow fluorescence and an upper band with a blue fluorescence. By continued elution 2·2 g. of 4-benzoylfluoranthene (see below) were obtained, which crystallised from ethanol in yellow, elongated prisms, m. p. 129—130° (Found : C, 90·22; H, 4·65. Calc. for $C_{23}H_{14}O$: C, 90·2; H, 4·6%). The blue fluorescent band was extracted with ethanol, and yielded 0·61 g. of 11-benzoylfluoranthene (see below), colourless hexagonal plates (ethanol) with blue fluorescence, m. p. 120—121° (mixed m. p. with 4-isomer 86—112°) (Found : C, 89·74; H, 4·6%). The lower half of the column on extraction with alcohol yielded 1·42 g. of a substance, which was chiefly the colourless isomer with a small quantity of the yellow compound. It appears that the two benzoylfluoranthenes are formed in approximately equal quantities.

(*b*) Benzoyl chloride (17·5 g.) was added dropwise to an ice-cold, stirred mixture of fluoranthene (25 g.) and aluminium chloride (17·5 g.) in carbon disulphide (150 c.c.), and the stirring continued for a further 8 hours at room temperature. The mixture was finally heated on the water-bath for 6 hours, the carbon disulphide removed by distillation, and the residue decomposed by ice. The resulting yellow solid was extracted with ether, washed first with sodium carbonate solution and then with water, and dried ($CaCl_2$). The ether was distilled off and left a dark yellow viscous mass (31 g.).

The product (5 g.) was separated chromatographically into fluoranthene (0·32 g.), 4-benzoylfluoranthene (1·55 g.), 11-benzoylfluoranthene (1·81 g.), and a mixture of the last two compounds (0·33 g.), thus showing again that the two isomers are formed in approximately equal quantities.

4-Benzoylfluoranthene.—The 2 : 4-*dinitrophenylhydrazone* was prepared by Brady's method but

required 9 hours' heating; it formed orange crystals (glacial acetic acid), m. p. 260—265° (decomp.) (Found: N, 11·7. $C_{28}H_{18}O_4N_4$ requires N, 11·53%). The *picrate* had m. p. 158—160° (Found: N, 8·00. $C_{39}H_{17}O_9N_3$ requires N, 8·42%). The *oxime*, prepared by refluxing 4-benzoylfluoranthene (0·5 g.) with hydroxylamine hydrochloride (2 g.) in pyridine (10 c.c.) for 3 hours, formed plates from *iso*propanol, m. p. 219—223° (v. Braun and Manz, *loc. cit.*, give m. p. *ca.* 170°) (Found: N, 3·95. $C_{23}H_{15}ON$ requires N, 4·36%). The oxime (0·25 g.) and phosphorus pentachloride (0·5 g.) in anhydrous ether (45 c.c.) were kept for 20 hours, and the solution treated in the usual way to give an *anilide*, m. p. 260—263° (Found: N, 4·51. $C_{29}H_{18}ON$ requires N, 4·36%). 4-Benzoylfluoranthene gave no m. p. depression when mixed with a sample prepared from 4-cyanofluoranthene. Attempts to prepare the latter by refluxing 4-bromofluoranthene in pyridine with cuprous cyanide for 16 hours gave only unchanged material. It was obtained by the method of von Braun and Manz (*Annalen*, 1931, *loc. cit.*) and purified by successive crystallisation from ethanol and light petroleum (b. p. 60—80°) and chromatographic adsorption on alumina on which it separated as a greenish-yellow fluorescing band. Final crystallisation from light petroleum (b. p. 80—100°) gave a yellow solid, m. p. 117—121° (lit. 112°), evidently not quite pure (Found: N, 5·58. Calc. for $C_{17}H_9N$: N, 6·17%). 4-Cyanofluoranthene (0·63 g.) was dissolved in anhydrous benzene (25 c.c.) and added to the Grignard reagent prepared from magnesium (0·10 g.), bromobenzene (0·45 c.c.), and anhydrous ether (1·85 c.c.), and refluxed for 10 hours. It was then decomposed by crushed ice (15 g.) and 10% sulphuric acid (25 c.c.), and steam-distilled. The residue was extracted with ether, and the extract washed first with dilute sulphuric acid, then with water, and dried ($CaCl_2$). Evaporation gave an oily solid which was crystallised from ethanol; m. p. 125—129° (m. p. depression with 4-cyanofluoranthene). It was chromatographed in benzene on a column 12″ × 0·86″ and the yellow band eluted. 4-Benzoylfluoranthene was thus obtained which crystallised from ethanol in yellow needles, m. p. 129—130°.

Chromic acid (" A.R. ", 1·40 g.) in water (1 c.c.) and glacial acetic acid (1 c.c.) was slowly added to 4-benzoylfluoranthene (0·60 g.) in glacial acetic acid (10 c.c.). The mixture was kept overnight, then refluxed for 2 hours, poured into water (150 c.c.), and extracted with benzene, extraction of which with sodium hydroxide followed by acidification gave the yellow 2-*benzoylfluorenone*-1-*carboxylic acid*, m. p. 227—228° after purification *via* the barium salt and crystallisation from glacial acetic acid (Found: C, 74·64; H, 3·57. $C_{21}H_{12}O_4$ requires C, 76·83; H, 3·66%). The acid (0·01 g.) was heated with a trace of copper-bronze in quinoline for 10 minutes, and the mixture decomposed with hydrochloric acid. The mixture was extracted with benzene, which was then washed with water, dried (Na_2SO_4), and chromatographed on a column 4″ × 0·4″. Development with benzene gave a yellow band which was ultimately collected in the filtrate, and gave 2-benzoylfluorenone, bright yellow needles (from ethanol), m. p. 175—176°, no m. p. depression when mixed with a specimen prepared as follows. Sodium dichromate (0·185 g.) in glacial acetic acid (1 c.c.) and water (0·25 c.c.) was added to a gently boiling solution of 2-benzoylfluorene (0·1 g.) in glacial acetic acid (2 c.c.), and refluxed for 2½ hours. Dilution with water (20 c.c.) and extraction with benzene gave 0·07 g. of crude product which was dissolved in benzene, chromatographed on a column 4″ × 0·4″, and developed with 3 : 1 benzene–light petroleum (b. p. 80—100°). A deep yellow eluate was obtained which yielded 2-benzoylfluorenone, m. p. 175—177°, after crystallisation from ethanol (Found: C, 84·3; H, 4·5. Calc. for $C_{20}H_{12}O_2$: C, 84·5; H, 4·2%).

11-Benzoylfluoranthene (0·90 g.) was oxidised by chromic acid ("A.R", 2·1 g.) in water (1·5 c.c.) and glacial acetic acid (1·5 c.c.) in the same way as the 4-isomer, and gave 7-*benzoylfluorenone*-1-*carboxylic acid*, m. p. 206—209° (m. p. 184—195° when mixed with 2-benzoylfluorenone-1-carboxylic acid), obtained as a yellow solid (Found: C, 76·83; H, 3·81. $C_{21}H_{12}O_4$ requires C, 76·83; H, 3·66%), 0·05 g. of which was decarboxylated as above to give 2-benzoylfluorenone, m. p. 174—176°, no m. p. depression with an authentic sample.

Acetylation of Fluoranthene.—Fluoranthene was acetylated by acetyl chloride and aluminium chloride by the method of Buu-Hoï and Cagniant (*loc. cit.*), and a crude orange oily solid (18 g.) obtained. The product (1 g.) was converted into a picrate, which after crystallisation from methanol had m. p. 174—181° and when decomposed gave fluoranthene. Chromatographic separation was then attempted; the crude solid (1·5 g.) was dissolved in benzene, chromatographed on a column (24·5″ × 0·86″), and developed with benzene. A blue fluorescing filtrate gave 0·88 g. of fluoranthene, leaving on the column a lower yellow band at the foot, an intermediate blue fluorescent band, and a dark band at the top. The yellow band gave 0·19 g. of 4-*acetylfluoranthene* (see below) which was crystallised from methanol; m. p. 128—129° (Found: C, 88·16; H, 4·75. $C_{18}H_{12}O$ requires C, 88·53; H, 4·92%). The blue fluorescent band gave 0·22 g. of pale yellow plates (methanol) of 11(?)-*acetylfluoranthene*, m. p. 101—102° (Found: C, 88·44; H, 5·21%). From the top of the column 0·15 g. of an uncrystallisable oil was obtained.

The remainder of the crude acetylation product (16 g.) and picric acid (10 g.) were dissolved in boiling ethanol. Decomposition of the resultant picrate gave fluoranthene (7 g.), and the alcoholic filtrate on the usual treatment gave a mixture of acetylfluoranthenes (3·8 g.) which when chromatographed gave fluoranthene (1·91 g.), 4-acetylfluoranthene, m. p. 125—129° (0·09 g.), a mixture of acetylfluoranthenes, m. p. 90—101° (1·08 g.), and a *diacetylfluoranthene*, yellow needles (from ethanol–acetic acid), m. p. 140—142° (Found: C, 83·6; H, 5·25. $C_{20}H_{14}O_2$ requires C, 83·9; H, 4·89%).

4-*Acetylfluoranthene*.—The 2 : 4-*dinitrophenylhydrazone*, formed easily by Allen's method as a red solid, was purified by being boiled with ethanol–acetic acid, m. p. 261—262° (Found: N, 14·3. $C_{24}H_{16}O_4N$ requires N, 13·2%). The *oxime*, prepared by refluxing the compound (0·06 g.) in pyridine (2·4 c.c.) with hydroxylamine hydrochloride (0·24 g.) for 7 hours, adding water, and crystallising the precipitate from ethanol, had m. p. 196—198° (Found: N, 4·67. $C_{18}H_{13}ON$ requires N, 5·41%). 4-Acetylfluoranthene was shown to be identical with a specimen prepared as follows. 4-Cyanofluoranthene (0·15 g.) in benzene (25 c.c.) was added to the Grignard reagent prepared from magnesium (0·10 g.) and methyl iodide (0·60 g.) in ether, and the mixture boiled under reflux for 40 hours. The product, obtained by the usual procedure, was dissolved in benzene and chromatographed on a column 5·5″ × 0·53″ and developed with benzene containing 1% of ethanol. A yellow band separated, and finally was filtered and evaporated. The dirty yellow residue was triturated with methanol and dissolved in the minimum amount of ethanol. The cold solution was filtered, and the filtrate on reduction to ⅓ of its volume gave a pale yellow solid,

m. p. 122—128°, which was dissolved in benzene and chromatographed on a column 8″ × 0·53″. Development with benzene gave a yellow band which was eluted and gave 4-acetylfluoranthene, m. p. 131—132°, yellow needles (from ethanol), showing no m. p. depression when mixed with the higher melting isomer from the Friedel–Crafts reaction.

11(?)-*Acetylfluoranthene*.—The 2 : 4-*dinitrophenylhydrazone*, obtained easily by Allen's method, was triturated with boiling ethanol–acetic acid; it sublimed in orange needles, m. p. 299—301° (Found: N, 12·8%). The *oxime*, prepared as above, was crystallised from glacial acetic acid containing a little ethanol, and then had m. p. 173—178° (with sublimation) (Found: N, 5·56%).

Phthaloylation of Fluoranthene.—Fluoranthene (20 g.) was treated with phthalic acid as described by von Braun and Manz (*Annalen*, 1932, *loc. cit.*), and 14 g. of crude product obtained. It was too strongly adsorbed on alumina to be purified by chromatographic adsorption. The crude solid was dissolved in chloroform which on standing deposited a solid *A* (5 g.), m. p. 203—214°, and the mother liquor on evaporation gave a resinous solid *B* (7 g.), m. p. 158—185°. Fraction *A* (4·5 g.) was esterified with methanol and sulphuric acid to give a mixture of methyl esters (2 g.), m. p. 100—145°, which was chromatographed in benzene on a column 24″ × 0·86″ and developed with 3 : 1 benzene–light petroleum (b. p. 80—100°). Two blue fluorescent bands separated by a deep yellow fluorescent band resulted, and were successively collected in the filtrate. The first blue band gave 0·09 g. of oily solid, and the yellow band gave 0·70 g. of *methyl 4-benzoylfluoranthene-2′-carboxylate*, yellow crystals, m. p. 103—105°, after crystallisation from light petroleum (b. p. 100—120°) (Found: C, 82·66; H, 4·64. $C_{25}H_{16}O_3$ requires C, 82·41; H, 4·39%). The upper band yielded 0·65 g. of *methyl 11-benzoylfluoranthene-2′-carboxylate*, yellow crystals with blue fluorescence, m. p. 172—174° after crystallisation from light petroleum (b. p. 100—120°) (Found: C, 81·79; H, 4·48%). Fraction *B* (5 g.) was chromatographed similarly on a column 24″ × 0·86″ and gave an uncrystallisable oil (0·34 g.), methyl 4-benzoylfluoranthene-2′-carboxylate, m. p. 101—103° (1·15 g.), and a mixture (1·72 g.), m. p. 120—160°, consisting mainly of the isomeric ester.

Methyl 4-benzoylfluoranthene-2′-carboxylate was hydrolysed with 10% sodium hydroxide and the resulting 4-benzoylfluoranthene-2′-carboxylic acid crystallised from glacial acetic acid; it formed bright yellow needle-prisms, m. p. 231—232° (lit. 230°) (Found: C, 81·66; H, 4·09. Calc. for $C_{24}H_{14}O_3$: C, 82·28; H, 4·00%). The oxime had m. p. 221—225° (lit. 207—209°) (Found: N, 3·60. Calc. for $C_{24}H_{15}O_3N$: N, 3·83%). The acid (0·05 g.) was heated with a trace of copper in quinoline at 195° for 10 minutes, and the precipitate, obtained by the addition of dilute hydrochloric acid, dissolved in benzene and chromatographed on a column 3·75″ × 0·4″. Development with 3 : 1 benzene–light petroleum (b. p. 80—100°) gave a yellow band which on elution yielded 4-benzoylfluoranthene, yellow needles (ethanol), m. p. 129—130°; this gave no m. p. depression when mixed with authentic sample.

Methyl 11-benzoylfluoranthene-2′-carboxylate, m. p. 172—174°, was hydrolysed more slowly (4 hours) than the isomer, and gave 11-benzoylfluoranthene-2′-carboxylic acid, m. p. 227—228° (lit. 212°), depressed by the 4-isomer (Found: C, 82·39; H, 4·03. Calc. for $C_{24}H_{14}O_3$: C, 82·28; H, 4·00%). Decarboxylation as above for 20 minutes at 175—180°, and adsorption of the product on a column 3·5″ × 0·40″, gave a blue fluorescent band which on elution with alcohol gave 11-benzoylfluoranthene, colourless plates, m. p. 117—119°, not depressed by an authentic sample. The oxime formed compact prisms (from benzene), m. p. 232—235° (lit. 224—225°).

Fluoranthenecarboxylic Acid by the Friedel–Crafts Reaction.—The crude product (17 g.) obtained by treating fluoranthene with oxalyl chloride according to the method of von Braun and Manz (*loc. cit.*) was refluxed with methanol (350 c.c.) and concentrated sulphuric acid (35 c.c.) for 5 hours, filtered from unchanged acids, and poured into water. The resulting oil was extracted with ether, the ether layer washed with sodium carbonate solution, and dried, and the ether removed by distillation, leaving a solid (5·13 g.), m. p. 75—90°. The solid was dissolved in benzene, chromatographed on a column 30″ × 0·86″, and developed with 3 : 1 benzene–light petroleum (b. p. 80—100°). Two bands containing the main products resulted: (*a*) a lower yellow band, (*b*) an upper band with a deep yellow fluorescence. Band (*a*) gave methyl fluoranthene-11-carboxylate (2·58 g.), m. p. 93—95° after crystallisation from ethanol (Found: C, 82·33; H, 4·90. $C_{18}H_{12}O_2$ requires C, 83·08; H, 4·61%), and (*b*) gave *dimethyl fluoranthenedicarboxylate* (1·33 g.), deep yellow crystals (ethanol), m. p. 183—185° (Found: C, 75·3; H, 4·60. $C_{20}H_{14}O_4$ requires C, 75·5; H, 4·40%).

Methyl fluoranthene-11-carboxylate was hydrolysed by being heated for 1 hour with 10% sodium hydroxide, and worked up in the usual way. Fluoranthene-11-carboxylic acid separated as colourless needles (glacial acetic acid), m. p. 278—280° subliming at 220° (Found: C, 82·6; H, 4·35. Calc. for $C_{17}H_{10}O_2$: C, 82·9; H, 4·06%). It gave a m. p. depression when mixed with fluoranthene-4-carboxylic acid (see below), and was not decarboxylated when heated with quinoline and copper bronze for ½ hour at 235°.

4-Cyanofluoranthene (0·1 g.) was heated in a sealed tube with concentrated hydrochloric acid (10 c.c.) for 16 hours at 200°; the product gave fluoranthene-4-carboxylic acid, yellow crystals (glacial acetic acid), m. p. 281—288° (lit. 264—275°).

Dimethyl fluoranthenedicarboxylate was similarly hydrolysed (3 hours), and *fluoranthenedicarboxylic acid* obtained as yellow needles by sublimation, m. p. >350° (Found: C, 72·9; H, 4·18. $C_{18}H_{10}O_4$ requires C, 74·5; H, 3·45%). The analysis shows that the acid is not pure, and this was confirmed by decarboxylation in quinoline at 235° with copper bronze for ½ hour. A micro-sublimation gave first a little fluoranthene, and later almost colourless needles of fluoranthene-11-carboxylic acid, m. p. 276—279°, not depressed by a sample of the above mono-acid. Fluoranthene-11-carboxylic acid is not decarboxylated under the above conditions, but the 4-acid readily gives fluoranthene when heated in quinoline at 200—205° with copper for 20 minutes.

Fluoranthenecarboxylic Acids by the Houben Reaction.—Aluminium chloride (16 g.) was gradually added to fluoranthene (20 g.) and trichloromethyl cyanide (17·4 g.) in chlorobenzene (160 c.c.), and the mixture then saturated with hydrogen chloride. The temperature was raised to 100° during an hour, and kept there for 1 hour with frequent shaking. Decomposition of the product with excess of concentrated hydrochloric acid followed by steam-distillation gave a dark residue which was treated with

concentrated hydrochloric acid, collected, and washed free from acid. The crude solid was heated with sodium hydroxide solution and filtered, leaving a dark sludge which was thoroughly washed. Acidification of the filtrate and the washings with hydrochloric acid gave the crude mixture of acids which was washed, dried, and refluxed with methanol (400 c.c.) and concentrated sulphuric acid (40 c.c.) for 5 hours. The mixture was filtered, the filtrate poured into water, and the precipitate extracted with ether. Evaporation gave a pale yellow solid (5 g.) which was dissolved in benzene, chromatographed on a column 20·5″ × 0·86″, and developed with 3 : 1 benzene–light petroleum (b. p. 80—100°). A yellow band separated, and was eluted with ethanol, yielding methyl fluoranthene-11-carboxylate (3·78 g.), m. p. 96—97°, identical with a specimen prepared as above. It was hydrolysed to the acid by being heated with 10% sodium hydroxide. The dark sludge (above) was dried and refluxed with methanol (250 c.c.) and concentrated sulphuric acid (25 c.c.) for 5 hours. Working up as before gave 3·69 g. of methyl fluoranthene-11-carboxylate.

Benzoylation of Naphthalene in Nitrobenzene.—A clear solution was obtained by gently warming benzoyl chloride (11·5 c.c.), powdered aluminium chloride (14 g.), and nitrobenzene (80 c.c.). Naphthalene (12·8 g.) was added slowly, and the solution heated at 60° for 20 minutes. The mixture was poured into water and steam-distilled, leaving a dark oil which was extracted with ether. The ether solution was washed successively with water, sodium carbonate solution, and water, and dried ($CaCl_2$). The ether was distilled off and the residual dark red oil chromatographed on a column 21″ × 0·86″. Development with ether gave a red band which was finally collected in the filtrate, from which a solid (15 g.), melting over a wide range, was obtained. It was chromatographed in benzene on a column 24·5″ × 1·18″, and developed with 3 : 1 benzene–light petroleum (b. p. 40—60°); the product melted at 71—75°, and was shown to consist of 1- and 2-benzoylnaphthalenes in the ratio 2 : 1 by a further chromatographic separation. Further elution of the column with ethanol gave 2-benzoylnaphthalene (4·75 g.), m. p. 75—80°, colourless needles (from light petroleum, b. p. 60—80°). The yield ratio of 1- and 2-benzoylnaphthalene is thus approximately 46 : 54. 1-Benzoylnaphthalene was also prepared from 1-cyanonaphthalene (5·75 g.) in anhydrous ether (75 c.c.) and the Grignard reagent prepared from magnesium (1·0 g.), bromobenzene (4·45 c.c.), and ether (18·5 c.c.), by refluxing for ½ hour. The mixture was decomposed with 10% sulphuric acid (25 c.c.) and ice (15 g.), steam-distilled, and the residue worked up to give 1-benzoylnaphthalene, m. p. 74—76° after crystallisation from light petroleum (b. p. 60—80°). The 2 : 4-*dinitrophenylhydrazone* separated after 15 minutes when Brady's method was used. It was crystallised from ethanol–acetic acid, m. p. 248—249° (Found : N, 13·8. $C_{23}H_{16}O_4N_4$ requires N, 13·6%). 2-Benzoylnaphthalene, prepared similarly, gave a 2 : 4-*dinitrophenylhydrazone*, m. p. 232—233° (lit., 257—258°) (Found : N, 14·5%). 2-*Benzoylfluorene dinitrophenylhydrazone*, orange prisms (from glacial acetic acid), had m. p. 265° (Found : N, 12·2%. $C_{36}H_{18}O_4N_4$ requires N, 12·4%).

Benzoylation of 1 : 2 : 3 : 4-*Tetrahydrofluoranthene.*—Tetrahydrofluoranthene (11 g.) was added slowly to benzoyl chloride (8 g.) and aluminium chloride (8 g.) in carbon disulphide (60 c.c.), and the mixture decomposed and worked up to give a crude product (11 g.). By a series of long and tedious chromatographic separations four products were isolated. (*a*) Unchanged tetrahydrofluoranthene. (*b*) 5-*Benzoyl*-1 : 2 : 3 : 4-*tetrahydrofluoranthene* (60% yield), which formed pale yellow prisms (ethanol), m. p. 144—145° (Found : C, 88·59; H, 5·75. $C_{23}H_{18}O$ requires C, 89·0; H, 5·81%). The compound (1 g.) was refluxed for 24 hours in sulphur-free xylene (20 c.c.) with chloranil (1·6 g.), an equal volume of ether added, and the tetrachloroquinol extracted with dilute sodium hydroxide. The xylene–ether layer was washed free from alkali and dried ($CaCl_2$); the solution on evaporation gave a yellow solid, m. p. 123—126°, which was chromatographed in benzene on a column 10·5″ × 0·86″ and developed with 3 : 1 benzene–light petroleum (b. p. 80—100°). The yellow filtrate yielded 4-benzoylfluoranthene (0·65 g.), m. p. 131—132° after crystallisation from ethanol. 5-Benzoyltetrahydrofluoranthene does not form a picrate, and the 2 : 4-*dinitrophenylhydrazone* could not be prepared by Allen's method, but was obtained in an impure form by Brady's method after 12 hours' boiling under reflux; it was an orange solid (from ethanol–acetic acid), m. p. 216—217° (Found : N, 10·0. $C_{29}H_{22}O_4N_4$ requires N, 11·43%). (*c*) An isomeric benzoyltetrahydrofluoranthene which was isolated as the orange 2 : 4-*dinitrophenylhydrazone* by Brady's method (Allen's method unsuccessful), m. p. >350° (Found : N, 11·40%). (*d*) A small quantity of an impure yellow *dibenzoyltetrahydrofluoranthene*, which had m. p. 173—178° (Found : C, 87·06; H, 4·80. $C_{30}H_{18}O_2$ requires C, 87·80; H, 4·39%).

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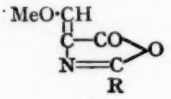
80. *Attempted Syntheses of Penicillin Homologues.*

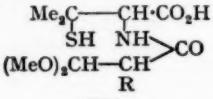
By WILSON BAKER AND W. D. OLLIS.

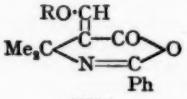
Attempts have been made to synthesise penicillins in which the *C*-formylglycine part of the molecule is replaced by either *C*-β-amino-α-formyl-*n*-butyric or -*iso*valeric acid residues. β-Benzamido*iso*valeric acid is converted by acetic anhydride into the 1 : 3-oxazine (IV), a type of compound analogous to the oxazolones derived from the *N*-acyl-α-amino-acids. The lactone group in (IV) is highly reactive, but the methylene group is inert and could not be condensed with ethyl orthoformate to give (III; R = Et), which might yield a penicillin on condensation with D-penicillamine. An alternative route started from *methyl β-benzamido-n-butyrate* which was formylated, converted into the *dimethylacetal*, and thence *via* the related *hydrazide* into the azide, which reacted with D-penicillamine giving the *acetal* (II; R = Ph·CO·NH·CHMe). A similar series of reactions starting from *methyl β-phenylacetamido-n-butyrate* gave the two racemic forms of the related *dimethylacetal* and of the *hydrazide*, each of which was converted into an azide and finally into the *N-acyl-D-penicillamine* derivatives

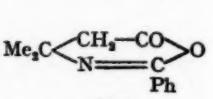
(II; R = Ph·CH_2·CO·NH·CHMe). Attempted thermal ring closure of the acetals (II) gave products devoid of antibacterial activity.

Of the numerous attempts which have been made to synthesise penicillins (see "Monograph on Penicillin"), only the interaction of certain 2-substituted 4-alkoxy (usually methoxy)-methylene-4 : 5-dihydro-oxazole-5-ones (I) with D-penicillamine has consistently given products showing antibiotic activity of the penicillin type (method *a*). By the condensation of 2-benzyl-4-methoxymethylene-4 : 5-dihydro-oxazole-5-one (I; R = CH_2Ph) with D-penicillamine, benzylpenicillin has been synthesised and isolated, though in extremely small yield (see du Vigneaud, Carpenter, Holley, Livermore, and Rachele, *Science*, 1946, **104**, 431, where previous references are given).


(I.)


(II.)


(III.)


(IV.)

Another reaction which has been claimed to give a product showing weak antibacterial properties is the thermal ring closure of the acetal (II; R = NH·CO·CH_2Ph) (method *b*) (Squibb Institute for Medical Research, Committee for Penicillin Synthesis Reports, CPS, 1945, 414, 452), but the precise conditions necessary to produce biologically-active material have not been defined, and a repetition of the work (Dr. J. F. W. McOmie, Bristol, and Drs. E. P. Abraham and E. B. Chain, Oxford, unpublished experiments) gave only inactive products.

The present work was designed to effect the synthesis of some penicillin homologues, in which the usual penaldic acid portion of the molecule, R·CO·NH·CH(CHO)·CO_2H, which is an α-amino-acid derivative, is replaced by the homologous β-amino-acid grouping R·CO·NH·CR′Me·CH(CHO)·CO_2H (R′ = H or Me). In these cases the penicillins, if produced, would possess the grouping R·CO·NH·CR′Me attached to the β-lactam ring instead of R·CO·NH, and as it is well known that considerable modifications of this part of the molecule are possible without loss of antibacterial properties it is quite possible that such homologous penicillins would be biologically active.

The first experiments were designed to synthesise by method (*a*) a penicillin in which the penaldic acid grouping is replaced by β-benzamido-α-formyl*iso*valeric acid,

Ph·CO·NH·CMe_2·CH(CHO)·CO_2H.

The synthesis of the required 6-keto-2-phenyl-4 : 4-dimethyl-5-alkoxymethylene-5 : 6-dihydro-1 : 3-oxazine (III) was, therefore, attempted. β-Benzamido*iso*valeric acid,

Ph·CO·NH·CMe_2·CH_2·CO_2H,

was first prepared by the benzoylation of β-amino*iso*valeric acid (Slimmer, *Ber.*, 1902, **35**, 408), but a better method is to benzoylate ethyl β-amino*iso*valerate, and hydrolyse the resulting *ethyl* β-*benzamidoisovalerate*. By treating β-benzamido*iso*valeric acid with acetic anhydride the liquid anhydro-derivative *6-keto-2-phenyl-4 : 4-dimethyl-5 : 6-dihydro-1 : 3-oxazine* (IV) is obtained. This 1 : 3-oxazine, when exposed to air or when treated with water, undergoes slow hydration with regeneration of the solid parent acid, but the reaction is catalysed by hydrogen ions, and occurs in a few seconds in presence of dilute hydrochloric acid. The 1 : 3-oxazine (IV) reacts slowly with ethyl alcohol to give ethyl β-benzamido*iso*valerate, but it reacts immediately with aniline in ethereal solution to give *β-benzamidoisovaleranilide*. Unlike the related oxazolones derived from the α-amino-acids, the 1 : 3-oxazine (IV) does not possess a reactive methylene group, and attempts to effect condensation with either benzaldehyde, or with ethyl orthoformate in presence of acetic anhydride to give (III; R = Et) were unsuccessful. Again, no formylation occurred when ethyl β-benzamido*iso*valerate was treated with ethyl formate and potassium. The greater degree of reactivity of the methylene group in the oxazolones is to be ascribed to the fact that the methylene group is activated not only by the carbonyl but also by the ·N:C group. Moreover, in the 1 : 3-oxazine (IV) the CMe_2 group exerts a marked steric effect in diminishing reactivity at the adjacent methylene group (see below). In view of the failure to obtain the required alkoxymethylene-1 : 3-oxazine (III), this approach to the synthesis of a penicillin homologue had to be abandoned.

The 1 : 3-oxazine (IV) appears to represent a new type of anhydro-derivative not previously prepared from an amino-acid. Such 1 : 3-oxazines are only obtainable from β-amino-acids, but might arise by dehydration of, for example, *N*-acyl derivatives of aspartic acid, which is simultaneously an α- and a β-amino-acid.

Experiments were then directed towards the preparation of acetals of type (II; R =

CHMe·NH·COPh and CHMe·NH·CO·CH_2Ph) which, by thermal ring closure (method *b*), might be converted into homologues of phenylpenicillin and benzylpenicillin respectively. Ethyl β-amino-*n*-butyrate was treated with benzoyl chloride in pyridine, giving *ethyl β-benzamido-*n*-butyrate*. Reaction of this ester with aniline gave the corresponding *anilide*, and although when treated with potassium and ethyl formate it yielded a formyl derivative giving a 2 : 4-dinitrophenylhydrazone, it was found desirable, since ethyl β-amino-*n*-butyrate is not a very accessible compound, to devise an alternative route to compounds of this type. A solution of β-amino-*n*-butyric acid was prepared by heating crotonic acid with aqueous ammonia at 150°, and, without isolation, was treated with benzoyl chloride and alkali, yielding *β-benzamido-*n*-butyric acid*. The *methyl* ester of this acid was then formylated, and converted into the dimethylacetal, *methyl β-benzamido-α-dimethoxymethyl-*n*-butyrate*,

$$Ph{\cdot}CO{\cdot}NH{\cdot}CHMe{\cdot}CH(CO_2Me){\cdot}CH(OMe)_2 \quad (V.)$$

characterised as its *2 : 4-dinitrophenylhydrazone*. The ester (V) was now converted *via* the related hydrazide, $Ph{\cdot}CO{\cdot}NH{\cdot}CHMe{\cdot}CH(CO{\cdot}NH{\cdot}NH_2){\cdot}CH(OMe)_2$ (VI), into the corresponding acid azide, and condensation of the latter with D-penicillamine yielded N-(*β-benzamido-α-dimethoxymethyl-*n*-butyryl*)-D-*penicillamine* (II; R = Ph·CO·NH·CHMe).

A similar series of reactions was carried out starting from *β-phenylacetamido-*n*-butyric acid*, the *methyl* ester of which was formylated and converted into the acetal, *methyl β-phenylacetamido-α-dimethoxymethyl-*n*-butyrate*, $Ph{\cdot}CH_2{\cdot}CO{\cdot}NH{\cdot}CHMe{\cdot}CH(CO_2Me){\cdot}CH(OMe)_2$ (VII). The two possible racemic forms of the acetal (VII), which contains two dissimilar asymmetrical carbon atoms, were isolated and are referred to as the α- and β-forms. Each was converted into an individual hydrazide, giving the α- and β-*forms of β-phenylacetamido-α-dimethoxymethyl-*n*-butyrylhydrazide*, $Ph{\cdot}CH_2{\cdot}CO{\cdot}NH{\cdot}CHMe{\cdot}CH(CO{\cdot}NH{\cdot}NH_2){\cdot}CH(OMe)_2$ (VIII), and these were, in turn, separately converted into the acid azides and condensed with D-penicillamine. The α-hydrazide (VIII) thus gave in a crystalline form one of the four possible stereoisomeric forms of N-(*β-phenylacetamido-α-dimethoxymethyl-*n*-butyryl*)-D-*penicillamine* (II; R = $Ph{\cdot}CH_2{\cdot}CO{\cdot}NH{\cdot}CMe$); the β-hydrazide (VIII), however, gave a crystalline mixture of stereoisomerides of (II; R = $Ph{\cdot}CH_2{\cdot}CO{\cdot}NH{\cdot}CHMe$) which could not be separated. These acylpenicillamines (II), including that previously described having R = Ph·CO·NH·CHMe, are not very stable compounds and can seldom be satisfactorily crystallised and obtained in a state of analytical purity. They are all soluble in alkalis, give a blue colouration with ferric chloride showing the presence of the thiol group, and give 2 : 4-dinitrophenylhydrazones.

The three acylpenicillamines (II; R = Ph·CO·NH·CHMe, and both specimens having R = $Ph{\cdot}CH_2{\cdot}CO{\cdot}NH{\cdot}CHMe$) were kindly tested as intermediates in the possible production of antibiotics of the pencillin type by Dr. E. P. Abraham of the Sir William Dunn School of Pathology, Oxford. In each case (II) (10 mg.) was heated at (*a*) 110° for 10 minutes, (*b*) 130° for 10 minutes, (*c*) 130° for 10 minutes, followed by a temperature rise to 160° during 10 minutes. The products were stirred with M/5-phosphate buffer (pH 7) (1 c.c.) and the solutions tested for antibacterial activity against *Staphylococcus aureus* by the plate method. In no case was any antibacterial activity observed.

Experimental.

β-Benzamidoisovaleric Acid.—(*a*) β-Aminoisovaleric acid was prepared in excellent yield from ββ-dimethylacrylic acid (*Org. Synth.*, 1943, **23**, 27) by heating under pressure with concentrated aqueous ammonia (Slimmer, *loc. cit.*), but difficulty was encountered in preparing its benzoyl derivative by Slimmer's procedure. The following method gave a 25% yield. To a vigorously-stirred solution of β-aminoisovaleric acid (11·7 g.) in 2N-sodium hydroxide (50 c.c.) cooled in ice was slowly added benzoyl chloride (14·5 g.) and 2N-sodium hydroxide (50 c.c.) so that the mixture always remained alkaline. After an hour concentrated hydrochloric acid (20 c.c.) was added and the precipitate collected, washed with a little ether, and crystallised from water, giving β-benzamidoisovaleric acid (5·5 g.) as oblong plates, m. p. 141° (cf. Slimmer, *loc. cit.*).

(*b*) A mixture of ethyl β-benzamidoisovalerate (1 g.) (below) and N-potassium hydroxide (10 c.c.) was shaken for 1 hour at room temperature, filtered, and acidified, yielding β-benzamidoisovaleric acid (0·95 g.) as oblong plates from water, m. p. and mixed m. p. 141°.

Ethyl β-Benzamidoisovalerate.—β-Aminoisovaleric acid (11·7 g.) was converted by the method of Fischer (*Ber.*, 1901, **34**, 433) into ethyl β-aminoisovalerate (7·5 g.), b. p. 50°/4 mm. A mixture of ethyl β-aminoisovalerate (4·5 g.) and benzoyl chloride (3·7 c.c.) in anhydrous pyridine (20 c.c.) was kept overnight. After heating on a steam-bath for a further 20 minutes the product was poured into water (50 c.c.) and extracted twice with 50 c.c. portions of ether. The combined extracts were washed with 2N-hydrochloric acid (10 c.c.), 2N-sodium carbonate solution (10 c.c.), and finally with water, and then dried ($MgSO_4$). The ether was removed and the residue distilled under reduced pressure, giving a colourless oil, b. p. 158°/6 mm., which solidified on cooling (5·7 g.; 74%). Recrystallisation from light petroleum (b. p. 60—80°) gave *ethyl β-benzamidoisovalerate* as silky needles, m. p. 49° (Found: C, 67·3; H, 7·6; N, 6·0. $C_{14}H_{19}O_3N$ requires C, 67·3; H, 7·6; N, 5·6%).

6-Keto-2-phenyl-4 : 4-dimethyl-5 : 6-dihydro-1 : 3-oxazine (IV).—A mixture of β-benzamido*iso*valeric acid (2 g.) and acetic anhydride (6 c.c.) was heated on a steam-bath for 4 hours. After removal of low-boiling material under reduced pressure, the residual liquid (1·7 g.; 92%) distilled as a colourless oil, b. p. 110—111°/3 mm. (Found: C, 70·2; H, 6·2; N, 6·6. $C_{12}H_{13}O_2N$ requires C, 70·9; H, 6·4; N, 6·9%). When this *6-keto-2-phenyl-4 : 4-dimethyl-5 : 6-dihydro-1 : 3-oxazine* was treated with dilute mineral acid, it rapidly gave β-benzamido*iso*valeric acid, m. p. and mixed m. p. 141°. When the 1 : 3-oxazine (500 mg.) and absolute ethanol (0·7 c.c.) were refluxed for 2 hours, and excess of ethanol removed, a solid (510 mg.; 83%) was left, m. p. 47°; mixed m. p. with ethyl β-benzamido*iso*valerate 49°.

*β-Benzamido*isovaleranilide.—(*a*) Aniline (100 mg.) was added to a solution of the 1 : 3-oxazine (200 mg.) in ether (1 c.c.). White needles almost immediately began to separate and after 12 hours were collected (235 mg.; 80%) and crystallised from ethanol; fine needles, m. p. 170° (Found: C, 72·5; H, 6·7; N, 9·5. $C_{18}H_{20}O_2N_2$ requires C, 73·0; H, 6·8; N, 9·5%).

(*b*) β-Benzamido*iso*valeric acid (1 g.) and aniline (2 c.c.) were heated at 170—180° for 1 hour, poured into water, and acidified with hydrochloric acid. The precipitate was washed with sodium carbonate solution and water (yield, 1·3 g.); needles from ethanol, m. p. and mixed m. p. 170°.

Ethyl β-Benzamido-n-butyrate.—A mixture of ethyl β-amino-*n*-butyrate (9 g.; Décombe, *Ann. Chim. Phys.*, **1932**, **18**, 133) and benzoyl chloride (9·7 c.c.) in anhydrous pyridine (50 c.c.) was kept overnight, heated on a steam-bath for 1 hour, poured into water (100 c.c.), and extracted twice with ether (100 c.c.). The extracts were washed with 2N-hydrochloric acid, then with 2N-sodium hydroxide, and distilled, giving a colourless oil (9·4 g.; 58%), b. p. 158—160°/2 mm., which solidified on cooling. Recrystallisation from a large volume of light petroleum (b. p. 60—80°) gave *ethyl β-benzamido-n-butyrate* as a crystalline powder, m. p. 47·5° (Found: C, 66·6; H, 7·7; N, 6·9. $C_{13}H_{17}O_3N$ requires C, 66·4; H, 7·3; N, 6·0%).

This ester was converted into the *anilide*, which was crystallised from ethyl acetate and then from *iso*propanol, giving fine needles, m. p. 190° (Found: C, 73·2; H, 6·5; N, 9·6. $C_{17}H_{18}O_2N_2$ requires C, 72·4; H, 6·4; N, 9·9%).

β-Benzamido-n-butyric Acid.—A solution of β-amino-*n*-butyric acid was prepared by heating crotonic acid (40 g.) with concentrated ammonia (250 c.c.; *d* 0·880) for 24 hours at 150° (Engle, *Bull. Soc. chim.*, 1888, **50**, 102). Air was drawn through the solution to remove most of the free ammonia and the process completed by boiling. The aqueous solution was diluted (to 300 c.c.) and sodium hydroxide (60 g.) added. Benzoyl chloride (165 c.c.) and a solution of sodium hydroxide (70 g.) in water (350 c.c.) were then added simultaneously to the stirred solution at 0° so that it remained alkaline. After 3 hours the mixture was filtered, acidified, and kept overnight in a refrigerator, and the precipitate collected, dried, and extracted with hot light petroleum (b. p. 60—80°) to remove benzoic acid. The insoluble residue was crystallised from hot water (1 l.), giving *β-benzamido-n-butyric acid* (60 g.; 63%) as colourless needles, m. p. 151·5° (Found: C, 63·9, 64·0; H, 6·6, 6·3; N, 6·3. $C_{11}H_{13}O_3N$ requires C, 63·8; H, 6·3; N, 6·8%).

Methyl β-Benzamido-n-butyrate.—β-Benzamido-*n*-butyric acid (95 g.) was refluxed with anhydrous methanol (180 c.c.) containing hydrogen chloride (7·5 g.) for 8 hours. Excess of methyl alcohol was removed under reduced pressure, and the residue dissolved in chloroform and extracted with 2N-sodium carbonate solution (acidification gave 5·6 g. of the unchanged acid). The chloroform layer was dried ($MgSO_4$) and distilled, yielding a colourless oil, b. p. 165—166°/3 mm. (81 g.; 80%), which solidified on cooling. Recrystallisation from light petroleum (b. p. 60—80°) gave *methyl β-benzamido-n-butyrate* as fine needles, m. p. 83° (Found: C, 65·1; H, 6·8; N, 5·5. $C_{12}H_{15}O_3N$ requires C, 65·2; H, 6·8; N, 6·3%).

Methyl β-Benzamido-α-dimethoxymethyl-n-butyrate (V).—Powdered potassium (18 g.) was added to a suspension of methyl β-benzamido-*n*-butyrate (92 g.) in anhydrous ether (800 c.c.). After addition of anhydrous freshly-distilled methyl formate (125 c.c.) the mixture was stirred mechanically at 0° for 18 hours, when the potassium derivative had separated as a dark brown oil. The bottom layer was poured into a mixture of ice (200 g.), water (125 c.c.), and chloroform (100 c.c.). To this was added the aqueous layer obtained by shaking the ethereal extract with ice (50 g.) and water (50 c.c.); unchanged ester (28 g.) was recovered from this ethereal extract. The mixture was stirred and the chloroform layer discarded. More chloroform (100 c.c.) was added, and a mixture of concentrated hydrochloric acid (50 c.c.) and ice (25 g.) was added slowly with stirring. After several minutes the organic layer was separated and the aqueous layer extracted three times with 50 c.c. portions of chloroform. The chloroform extracts were combined, washed with water (50 c.c.), and dried ($MgSO_4$). Filtering, treatment with charcoal, and removal of the solvent at room temperature under diminished pressure gave methyl β-benzamido-α-formyl-*n*-butyrate (79 g.; 76%) as a pale yellow oil.

Saturated methanolic hydrogen chloride (35 c.c.) was added to a cooled solution of the formyl compound (79 g.) in absolute methanol (150 c.c.) and the mixture kept at 0° for 48 hours, after which hydrogen chloride and methanol were removed under reduced pressure. The oily residue was dissolved in ether (200 c.c.), the solution shaken with water (250 c.c.) and ice (125 g.), and the ethereal layer washed twice with ice cold 2N-sodium hydroxide and with water, and finally dried ($MgSO_4$), filtered, and the solvent removed under reduced pressure, giving somewhat crude *methyl β-benzamido-α-dimethoxymethyl-n-butyrate* (31·6 g.; 37%) as a colourless oil (Found: C, 59·3; H, 7·2; N, 4·2; OMe, 26·7. $C_{15}H_{21}O_5N$ requires C, 61·0; H, 7·1; N, 4·7; OMe, 31·1%). This acetal gave a *2 : 4-dinitrophenylhydrazone* which separated from methanol as fine yellow needles, m. p. 200° (decomp.) (Found: C, 53·3; H, 4·4; N, 15·9. $C_{19}H_{19}O_7N_5$ requires C, 53·1; H, 4·4; N, 16·3%).

β-Benzamido-α-dimethoxymethyl-n-butyryl Hydrazide (VI).—Enough methanol was added to methyl β-benzamido-α-dimethoxymethyl-*n*-butyrate (13·2 g.) and 96% hydrazine hydrate (4·5 c.c.) to give a homogeneous solution, and the mixture refluxed for 24 hours. On cooling, a crystalline solid separated; this was collected and washed with a little ethanol (yield, 8·6 g.; 66%). Recrystallisation from ethanol gave *β-benzamido-α-dimethoxymethyl-n-butyryl hydrazide* as fine white needles, m. p. 184·5° (Found: C, 56·4; H, 6·9; N, 14·0. $C_{14}H_{21}O_4N_3$ requires C, 56·9; H, 7·1; N, 14·2%).

N-(β-Benzamido-α-dimethoxymethyl-n-butyryl)-D-penicillamine (II; R = Ph·CO·NH·CHMe).—A solu-

tion of the above hydrazide (1 g.) in N/2-hydrochloric acid (10 c.c.) was treated at 0° with a solution of sodium nitrite (260 mg.) in water (8 c.c.). The azide immediately separated as a white microcrystalline solid, which was collected after 20 minutes, washed with water, and added to a solution of D-penicillamine hydrochloride (1·890 g.) and anhydrous sodium carbonate (1·350 g.) in water (25 c.c.). The mixture was stirred at 30—40° for 3 hours, and was then filtered from a small amount of solid: this crystallised from ethanol in fine, colourless needles, m. p. 148°; it gave a 2 : 4-dinitrophenylhydrazone and a negative test for sulphur, and analysis suggested it was the *urea* derivative $(Ph{\cdot}CO{\cdot}NH{\cdot}CHMe{\cdot}CH[CH(OMe)_2]{\cdot}NH)_2CO$ (Found: C, 61·4; H, 6·5; N, 9·6. $C_{27}H_{38}O_7N_4$ requires C, 61·2; H, 7·2; N, 10·6%). The filtrate was extracted with ether (25 c.c.), and the aqueous layer covered with ether (25 c.c.) and acidified with 2N-hydrochloric acid (15 c.c.). The ethereal layer was separated after shaking, and the aqueous layer extracted twice with ether (25 c.c. portions). The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure, leaving a white microcrystalline solid, m. p. 105—106° (decomp.) (715 mg.; 51%). This *compound* could not be recrystallised satisfactorily (Found: C, 53·6; H, 6·9; N, 8·4; S, 6·2; OMe, 12·3. $C_{19}H_{32}O_6N_2S$ requires C, 55·3; H, 6·8; N, 6·8; S, 7·7; OMe, 15·0%). It gave a 2 : 4-dinitrophenylhydrazone, is soluble in alkali, and gave a strong blue ferric chloride reaction.

*β-Phenylacetamido-*n*-butyric Acid.*—The phenylacetylation of β-amino-*n*-butyric acid was carried out in the same way as the benzoylation. A solution of the amino-acid, obtained from crotonic acid (40 g.), was diluted to 300 c.c., and sodium hydroxide (60 g.) was added. To this solution was added phenylacetyl chloride (185 c.c.) and a solution of sodium hydroxide (70 g.) in water (300 c.c.). The precipitate obtained on acidification was washed with cold benzene, giving a crude material (55 g.; 54%) which was crystallised from benzene and then from ethyl acetate. *β-Phenylacetamido-*n*-butyric acid* was obtained as a white microcrystalline powder, m. p. 108° (Found: C, 65·3; H, 6·8; N, 6·2. $C_{12}H_{15}O_3N$ requires C, 65·2; H, 6·8; N, 6·3%).

*Methyl β-Phenylacetamido-*n*-butyrate.*—The preceding acid (28 g.) in absolute methanol (250 c.c.) containing anhydrous hydrogen chloride (12·5 g.) was refluxed for 8 hours. The product was worked up as in the case of the corresponding benzoyl derivative, giving an oil, b. p. 171—172°/3 mm. (21·2 g.; 71%), which solidified. Crystallisation from light petroleum (b. p. 60—80°) gave *methyl β-phenylacetamido-*n*-butyrate* as fine needles, m. p. 50° (Found: C, 66·5; H, 7·3; N, 6·2. $C_{13}H_{17}O_3N$ requires C, 66·4; H, 7·2; N, 6·0%).

*α- and β-Forms of Methyl β-Phenylacetamido-α-dimethoxymethyl-*n*-butyrate* (VII).—Powdered potassium (7·3 g.) was added to a suspension of methyl β-phenylacetamido-*n*-butyrate (40 g.) in anhydrous ether (300 c.c.) and anhydrous redistilled methyl formate (26 c.c.) added. After being stirred at 0° for 18 hours, the potassium derivative was worked up to give methyl β-phenylacetamido-α-formyl-*n*-butyrate, as a pale yellow oil (38 g.; 85%) which was dissolved in anhydrous methanol (75 c.c.), treated with saturated methanolic hydrogen chloride (15 c.c.), and kept at 0° for 24 hours, after which the excess methanol and hydrogen chloride were removed under reduced pressure at 20°. The oily residue was shaken with ether (100 c.c.) and ice (100 g.), and the ethereal layer washed twice with 2N-sodium hydroxide (25 c.c.) and with water. When this ethereal solution was dried ($MgSO_4$), a solid separated on standing. The drying agent and the solid were collected, the magnesium sulphate dissolved in water, and the residue (3 g.; 7%) crystallised from water, leaving the *α-form* of *methyl β-phenylacetamido-α-dimethoxymethyl-*n*-butyrate* as fine, colourless needles, m. p. 112° (Found: C, 62·4; H, 7·6; N, 4·3. $C_{16}H_{23}O_5N$ required C, 62·1; H, 7·4; N, 4·5%).

Removal of the ether from the filtrate at room temperature gave a yellow oil which solidified on standing (26 g.; 58%). Recrystallisation from benzene–light petroleum (b. p. 60—80°) gave the *β-form* of (VII) as fine, colourless needles, m. p. 76° (Found: C, 62·1, 62·2; H, 7·2, 7·5; N, 4·2%).

*α-Form of β-Phenylacetamido-α-dimethoxymethyl-*n*-butyryl Hydrazide* (VIII).—Anhydrous methanol (1·0 c.c.) was added to the α-form of methyl β-phenylacetamido-α-dimethoxymethyl-*n*-butyrate (360 mg.) and 96% hydrazine hydrate (0·19 c.c.) to give a clear solution. Crystals soon separated, and after 48 hours solvent and excess of hydrazine were removed in a vacuum over concentrated sulphuric acid. The *β-phenylacetamido-α-dimethoxymethyl-*n*-butyryl hydrazide* crystallised from ethanol in fine, colourless needles, m. p. 188° (Found: C, 58·3, 58·5; H, 7·6, 7·5; N, 13·7. $C_{15}H_{23}O_4N_3$ requires C, 58·3; H, 7·4; N, 13·6%).

α-Form of N-(*β-Phenylacetamido-α-dimethoxymethyl-*n*-butyryl*)-D-*penicillamine* (II; R = $Ph{\cdot}CH_2{\cdot}CO{\cdot}NH{\cdot}CHMe$).—This was prepared from the above hydrazide (1·050 g.) as in the case of the corresponding benzoyl derivative (II; R = Ph·CO·NH·CHMe) (above). The crude N-(*β-phenylacetamido-α-dimethoxymethyl-*n*-butyryl*)-D-*penicillamine* (1·120 g.; m. p. 152—154°) was crystallised from aqueous ethanol, giving needles, m. p. 185° (Found: C, 57·1; H, 6·8; N, 5·9; S, 6·2; OMe, 10·1. $C_{20}H_{30}O_6N_2S$ requires C, 56·3; H, 7·0; N, 6·6; S, 7·5; OMe, 11·6%). It gave a 2 : 4-dinitrophenylhydrazone, was soluble in alkali, and gave a strong blue ferric chloride reaction.

*β-Form of β-Phenylacetamido-α-dimethoxymethyl-*n*-butyryl Hydrazide* (VIII).—The *β-form* was prepared as in the case of the α-form, and after crystallising from ethanol was obtained as fine needles, m. p. 181° (Found: C, 58·2; H, 7·4; N, 13·7. $C_{15}H_{23}O_4N_3$ requires C, 58·3; H, 7·4; N, 13·6%).

β-Form of N-(*β-Phenylacetamido-α-dimethoxymethyl-*n*-butyryl*)-D-*penicillamine* (II; R = $Ph{\cdot}CH_2{\cdot}CO{\cdot}NH{\cdot}CHMe$).—This was prepared as in the case of the benzoyl derivative (II; R = Ph·CO·NH·CHMe). The crude material, having m. p. *ca.* 80° (decomp.) after shrinking from 60°, could not be crystallised satisfactorily and was analysed directly (Found: N, 7·4; S, 5·9; OMe, 13·6. $C_{20}H_{30}O_6N_2S$ requires N, 6·6; S, 7·5; OMe, 14·6%).

It gave a 2 : 4-dinitrophenylhydrazone, was soluble in alkali, and gave a strong blue ferric chloride reaction.

The authors' thanks are due to the Colston Research Society and to Imperial Chemical Industries Ltd. for grants which have defrayed part of the cost of this investigation.

THE UNIVERSITY, BRISTOL. [*Received, May 10th,* 1948.]

81. *Reactions of αβ-Unsaturated Cyclic Aldehydes and Ketones. Part VII. Alcohols derived from Phellandral.*

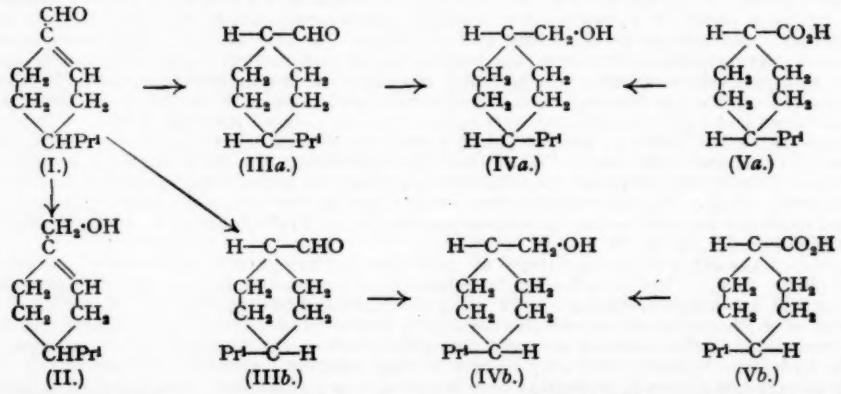
By J. P. E. Human, A. Killen Macbeth, and H. J. Rodda.

Phellandrol (4-*iso*propyl*cyclo*hex-1-enyl-1-carbinol) has been prepared by the Ponndorf reduction of phellandral, and characteristic derivatives are described. Dihydrophellandral and dihydrophellandrols have also been prepared, and the epimeric forms identified by their relationship to the 4-*iso*propyl*cyclo*hexyl-1-carbinols and corresponding carboxylic acids.

The study of alcohols related to simple carbonyl compounds isolated from natural products was undertaken some time ago with a view to the later identification of the alcohols in the essential oils themselves. In previous papers cumyl alcohol (*J.*, 1938, 1825) and the alcohols related to cryptone, 4-*iso*propyl*cyclo*hex-2-en-1-one (*J.*, 1938, 1820; 1939, 264, 518, 1531; 1948, 996), were described; and the reduction products of phellandral have now been examined.

The structure of phellandral has been established (*J.*, 1940, 808; 1946, 145) as 4-*iso*propyl-*cyclo*hex-1-en-1-aldehyde (I). Reduction by aluminium *iso*propoxide gives a crude alcohol from which, on repeated crystallisation of the *p*-nitrobenzoate and hydrolysis, pure phellandrol (II) is isolated in a yield approaching 50% of the crude material. The *p*-nitrobenzoate was found to be the best derivative for purification, although in the earlier experiments the hydrogen phthalate was used with fair success. In some of the Ponndorf reductions a higher-boiling fraction was isolated which was considered to be *diphellandryl ether*.

Phellandrol has b. p. 114°/5 mm., 122°/7 mm.; $\alpha_D^{24°}$ −99·5° (homogeneous; $l = 1$ dm.); $d_{20°}^{20°}$ 0·9311; $d_4^{20°}$ 0·9252; $n_D^{20°}$ 1·4826. It gives a p-*nitrobenzoate*, a 3 : 5-*dinitrobenzoate*, a *phenylurethane*, and an *α-naphthylurethane*.



Dihydrophellandral was prepared by the catalytic hydrogenation of phellandral, using palladised charcoal. It can exist in two epimeric forms (III*a* and *b*), and two semicarbazones were readily isolated by fractional crystallisation. Cooke and Macbeth (*J.*, 1939, 1245) prepared and characterised the 4-*iso*propyl*cyclo*hexan-1-carboxylic acids (V*a* and *b*) and related carbinols (IV*a* and *b*) by hydrogenation of cuminic acid, and reduction of the epimeric esters of the hexahydrocuminic acids. These substances are therefore available for determining the configurations of the dihydrophellandrals and dihydrophellandrols. The dihydrophellandral samples regenerated from the two semicarbazones were both found to give *trans*-hexahydrocuminic acid (V*b*) on oxidation, and the semicarbazones would therefore appear to be derived from the same epimeric form of the aldehyde. The less soluble derivative, trans-4-iso*propyl*cyclo*hexen*-1-*aldehyde α-semicarbazone*, has m. p. 173°, and the more soluble β-*semicarbazone* melts at 139°. Dihydrophellandral was further characterised by a p-*nitrophenylhydrazone*, mustard-coloured needles, melting at 161°.

Samples of dihydrophellandrol were derived in three ways, namely, (*a*) the Ponndorf reduction of dihydrophellandral, (*b*) the hydrogenation of dihydrophellandral using platinum oxide (Adams) as catalyst, and (*c*) catalytic hydrogenation in the presence of Raney nickel. In all cases mixtures of the epimeric alcohols were obtained, the *cis*-form being identified by the *p*-nitrobenzoate (m. p. 54—55°) and the 3 : 5-dinitrobenzoate (m. p. 72°), whilst the presence of the *trans*-form was detected by the characteristic curved laths of the 3 : 5-dinitrobenzoate (m. p. 95°). It would thus appear that the isolation of *trans*-dihydrophellandral from both

of the semicarbazones described above is probably due either to the removal of a more soluble *cis*-derivative during the crystallisations of the semicarbazones, or to the transmutation of a labile *cis*- to a more stable *trans*-form during the hydrolysis.

Experimental.

Ponndorf Reduction of Phellandral.—The phellandral used in the reductions was part of a supply obtained in a large-scale separation from *E. cneorifolia*, and had α_D −133° (homogeneous; $l = 1$ dm.). In a typical reduction a solution of redistilled aluminium *iso*propoxide in dry *iso*propyl alcohol (200 c.c. of M; 1·2 equivs.) was placed in a flask attached to a metre-long column packed with glass beads, and fitted with a reflux divider. A further quantity of solvent (100 c.c.) was added, and after the flask and contents had been heated in a bath at 160° the aldehyde (75 g.), in dry *iso*propyl alcohol (85 c.c.), was run in through a funnel fitted with a calcium chloride tube, at such a rate that steady boiling was maintained. Using a high reflux ratio acetone was slowly distilled off until (6 hours) the distillate was acetone free. Most of the *iso*propyl alcohol was then removed under reduced pressure through a short bead column, and the residue was cooled, light petroleum (200 c.c.; b. p. 50—80°) was added, followed by crushed ice (300 g.), and then sulphuric acid was added slowly (50 c.c., 10N; 2·6 equivs.). The light petroleum layer was separated, the acid layer washed again with the same solvent, and the total extract washed successively with water, sodium carbonate solution, and water (twice). After drying ($MgSO_4$), the solvent was removed, leaving crude phellandrol (75 g.).

The crude phellandrol may be converted into the *p*-nitrobenzoate for purification by repeated crystallisation, but it is better to carry out a preliminary purification by fractional distillation through a well-lagged, short, bead column. A main fraction (almost 65%) boiling at 94—97°/2·0 mm. was collected, and converted into the *p*-nitrobenzoate. In a typical experiment the phellandrol (25 g.) was placed in a 500 c.c. flask fitted with a mechanical stirrer and protected from moisture. Dry benzene (35 c.c.) and excess pyridine (40 c.c.) were added, and a solution of *p*-nitrobenzoyl chloride (30 g.) in warm, dry benzene (65 c.c.) was run in during half-an-hour, the mixture being cooled to about 25° when necessary. After being left for 12 hours the solution was acidified (hydrochloric acid, 33%, 40 c.c.; water 350 c.c.) to remove pyridine, the benzene layer was collected, and successively washed with water, 10% sodium carbonate solution, and water. After the benzene had been removed by steam distillation the residual oil crystallised on cooling, and the nitrobenzoate was dried on a porous tile, and recrystallised from light petroleum and finally from methanol–water. *Phellandryl* p-*nitrobenzoate* had m. p. 67°, $[\alpha]_D^{16°}$ −56·6° (*c*, 6·2, in chloroform) (Found: N, 4·6%. $C_{17}H_{21}O_4N$ requires N, 4·5%).

In a typical hydrolysis of the *p*-nitrobenzoate, the ester (20 g.) was dissolved in methanol (100 c.c.) containing potassium hydroxide (4·1 g.) and water (5 c.c.). After being heated under reflux on the steam-bath for an hour, about half of the methyl alcohol was removed under reduced pressure, the residue was steam-distilled, and the distillate extracted with light petroleum. After the solution had been dried ($MgSO_4$) and the solvent removed, pure phellandrol distilled (b. p. 114°/5 mm.), and had the following constants: $\alpha_D^{20°}$ −99·95° (homogeneous; $l = 1$ dm.); $\alpha_D^{24°}$ −99·45° (homogeneous; $l = 1$ dm.); $d_{20°}^{20°}$ 0·9311; $d_4^{20°}$ 0·9252; $n_D^{20°}$ 1·4826.

Phellandryl hydrogen phthalate. Phellandrol [18 g., $\alpha_D^{24°}$ −99·3 (homogeneous; $l = 1$ dm.)], phthalic anhydride (18 g.), and pyridine (60 c.c.) were heated with stirring for 6 hours at 60°. The resulting mixture was poured into sulphuric acid (10%, 600 c.c.), and extracted with ether. To the extract, mixed with crushed ice, about 90% of the theoretical amount of ice-cold sodium hydroxide solution was added with vigorous stirring, and the solution thereafter made alkaline with sodium carbonate. After the aqueous layer had been washed with ether it was acidified, and extracted with chloroform. A fine suspension of phthalic acid separated from the dried extract on standing, and after the solution had been centrifuged and the solvent removed the residual syrup crystallised on seeding. Yield 90%. Recrystallisation from light petroleum (40—60°) gave *phellandryl hydrogen phthalate* (11 g.) having m. p. 74°, $[\alpha]_D^{22°}$ −54·4 (*c*, 1·5, in chloroform) (Found: C, 71·45; H, 7·25. $C_{18}H_{22}O_4$ requires C, 71·45; H, 7·35%).

Phellandryl N-lævo*Menthylphthalamate.* A sample of phellandryl hydrogen phthalate (11 g.) was converted into the acid chloride by adding pyridine (2·95 g.) to a dry ethereal solution followed by the gradual addition of thionyl chloride (2·65 c.c.). The resultant mixture was treated with *lævo*menthylamine (6·62 c.c.) in pyridine (2·95 c.c.), and the crude *lævo*menthylphthalamate was obtained in over 80% yield. After recrystallisation from light petroleum (b. p. 60—90°) *phellandryl* N-lævo*menthylphthalamate* had m. p. 120° and $[\alpha]_D^{22°}$ −71·8° (Found: N, 3·25. $C_{28}H_{41}O_3N$ requires N, 3·2%). Hydrolysis of the menthylphthalamate by 10% methyl-alcoholic potassium hydroxide gave a sample of phellandrol (83% yield) after two distillations which had the same physical constants as the original alcohol.

To characterise phellandrol the following derivatives were also prepared. *Phellandryl phenylurethane*, recrystallised from light petroleum (60—90°), had m. p. 79°, $[\alpha]_D^{16°}$ −60·1° (*c*, 4·0, in chloroform) (Found: N, 5·2. $C_{17}H_{23}O_2N$ requires N, 5·15%). *Phellandryl α-naphthylurethane*, recrystallised from light petroleum, had m. p. 69·5°, $[\alpha]_D^{16°}$ −52·6° (*c*, 3·9, in chloroform) (Found: N, 4·4. $C_{21}H_{23}O_2N$ requires N, 4·35%). *Phellandryl* 3 : 5-*dinitrobenzoate* had m. p. 57·5°, $[\alpha]_D^{18°}$ −49·8° (*c*, 4·5, in chloroform) (Found: N, 8·15. $C_{17}H_{20}O_6N_2$ requires N, 8·05%).

Diphellandryl Ether.—In some of the Ponndorf reductions of phellandrol a higher-boiling component was isolated which appeared to be *diphellandryl ether*. In a typical case, after the reduction of phellandrol (90 g.) by the action of aluminium (6 g.) in *iso*propyl alcohol (300 c.c.) steam-distillation left a considerable amount of yellow polymerised product in the flask, and the distillate was extracted with ether. The extract, after being washed with sodium hydrogen sulphite solution (35%) and water, was dried (Na_2SO_4) and gave, on removal of the solvent, a first fraction (21 g.) boiling below 100°/1 mm., $n_D^{17°}$ 1·492. The residue, when transferred to a small flask and distilled over the open flame, gave a fraction, b. p. 170—180°/1 mm. It had $d_{19°}^{19°}$ 0·9351; $d_4^{19°}$ 0·9337; $n_D^{19°}$ 1·4986 and $[\alpha]_D$ −71·4° (homogeneous) (Found: C, 82·9; H, 11·6%. $C_{20}H_{34}O$ requires C, 82·7; H, 11·8%). The compound was unsaturated, and absorbed bromine readily, but no crystalline derivative could be isolated.

Dihydrophellandral.—Phellandral was hydrogenated to dihydrophellandral in the presence of palladised charcoal, and the reduction has been carried out both at atmospheric pressure and in a high-pressure bomb with an initial pressure of 70 atmospheres of hydrogen. In both cases an appreciable amount of higher-boiling by-product was formed. For purification an ethereal extract of the crude dihydrophellandral was shaken with concentrated sodium hydrogen sulphite solution (35%). The dihydrophellandral quickly formed a hydrogen sulphite compound which was filtered off within a few minutes (the higher-boiling impurity slowly forms a hydrogen sulphite compound on standing). The washed hydrogen sulphite cake was decomposed by steam-distillation with sodium carbonate, and the dihydrophellandral, extracted by ether from the distillate, had b. p. 57—59°/1 mm. when fractionated under reduced pressure.

Dihydrophellandral formed two *semicarbazones* which were separated by repeated fractional crystallisation from alcohol. The major product separated as feathery pearly crystals having m. p. 173° (Found: C, 62·7; H, 10·0; N, 20·0. $C_{11}H_{21}ON_3$ requires C, 62·6; H, 9·95; N, 19·9%). The more soluble component required more rigid purification, and was finally obtained as small granular crystals having m. p. 139° (Found: C, 62·65; H, 10·2; N, 20·0%).

In each case dihydrophellandral was regenerated from the semicarbazone (17 g.) by steam-distillation with dilute sulphuric acid (200 c.c., 10%). The aldehyde was extracted from the distillate with ether, dried ($MgSO_4$), and distilled, b. p. 61·5°/1·5 mm., n_D 1·4572 (yield, 8 g.). In both cases the recovered aldehyde gave, on oxidation, *trans*-hexahydrocuminic acid so that the two semicarbazones are apparently derived from *trans*-dihydrophellandral. The oxidation was conveniently carried out by dissolving the aldehyde (1·8 g.) in alcohol (60 c.c.), and adding a solution of silver nitrate (5·4 g.) in water (20 c.c.). Sodium hydroxide solution (100 c.c., N/2) was gradually added with shaking during ½ hour, and after further mechanical shaking the mixture was left overnight. After the precipitated silver had been removed, and washed, the filtrate was saturated with carbon dioxide, the alcohol distilled off, and the residue concentrated to about 100 c.c. On cooling and being acidified *trans*-hexahydrocuminic acid was precipitated, which gave a *p*-chlorophenacyl ester, m. p. 97·5°, which was not depressed on admixture with an authentic sample (Cooke and Macbeth, *loc. cit.*).

Although the semicarbazones provide evidence of the presence of *trans*-dihydrophellandral alone, the aldehyde must be a mixture of the epimeric forms as the alcohol obtained on reduction gave derivatives of both *cis*- and *trans*-forms. Dihydrophellandral was further characterised as the *p-nitrophenylhydrazone*, fine mustard-coloured needles, m. p. 161°, after crystallisation from methanol (Found: C, 66·3; H, 8·2; N, 14·4. $C_{16}H_{23}O_3N_3$ requires C, 66·4; H, 8·0; N, 14·5%).

Dihydrophellandrol.—(1) Dihydrophellandral (41 g.) was converted into the alcohol on Ponndorf reduction using aluminium foil (4 g.) dissolved in *iso*propyl alcohol (200 c.c.). After working up dihydrophellandrol (30 g.) was obtained, having b. p. 98°/1 mm. and $n_D^{20°}$ 1·4692. The alcohol consisted mainly of *cis*-4-*iso*propyl*cyclo*hexyl-1-carbinol as it gives a *p*-nitrobenzoate, m. p. 54—55° (Found: C, 66·7; H, 7·7; N, 4·6. Calc. for $C_{17}H_{23}O_4N$: C, 66·8; H, 7·6; N, 4·6%), and an α-naphthylurethane, m. p. 78° (Found: C, 77·65; H, 8·2; N, 4·35. Calc. for $C_{21}H_{27}O_2N$: C, 77·5; H, 8·35; N, 4·3%), which are identical with the *cis*-derivatives previously described (Cooke and Macbeth, *loc. cit.*). (The m. p. of the α-naphthylurethane was previously wrongly recorded.) The 3 : 5-dinitrobenzoate, m. p. 71—72°, is also derived from the *cis*-epimer, but some of the characteristic curved laths, m. p. 95°, of the *trans*-ester were also isolated.

(2) A sample of phellandral (20 g.) was hydrogenated in alcoholic solution (40 c.c.) containing Adams platinum oxide catalyst (0·3 g.), the initial hydrogen pressure of 820 lb. per sq. in. gradually falling during 2 hours to a final value of 520 lb. per sq. in. The product was poured into water and extracted with ether. The ether solution was washed with hydrogen sulphite solution to remove traces of aldehyde (2—3 g. of hydrogen sulphite compound) and subsequently worked up giving a sample (12 g.) of dihydrophellandrol which had b. p. 90—93°/0·5 mm. The alcohol consisted of both the *cis*- and the *trans*-form, the former being identified as the *p*-nitrobenzoate, m. p. 54—55°, the latter being isolated as the curved laths of the 3 : 5-dinitrobenzoate, m. p. 95°.

(3) Hydrogenation of phellandral in the presence of Raney nickel also gave a mixed dihydrophellandrol from which the same two derivatives were isolated.

We are indebted to the Commonwealth Research Fund which enabled two of us (H. J. R. and J. P. E. H.) to take part in this work.

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[*Received, May 13th*, 1948.]

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82. *Methylthio-derivatives of Benzophenone, Tetraphenylethylene, and Related Substances.*

By AHMED MUSTAFA.

1-Bromo-1 : 2-diphenyl-2-*p*-methylthiophenylethylene (II) and 1-phenyl-2 : 2-bis-*p*-methylthiophenylethylene (III) were prepared and tested for oestrogenic activity.

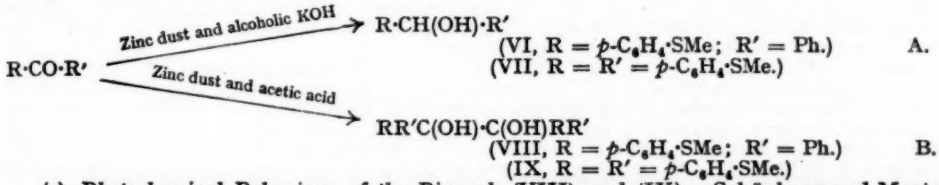
The alkaline and acid reductions of *p*-methylthiobenzophenone (IV) and bis-*p*-methylthiobenzophenone (V) (schemes A and B respectively) were studied and the photochemical behaviour of the solutions of the corresponding pinacols (VIII and IX) in acetone is described.

Some reactions of (IV), (V), and bis-*p*-methylthiobenzophenone chloride are given.

(*a*) IN view of the remarkable oestrogenic activity of chlorotriphenylethylene and its analogues (Robson, Schönberg, and Fahim, *Nature*, 1938, **142**, 292; Robson, Schönberg, Tadros, and

Fahim, *J.*, 1940, 1327; Schönberg, Robson, and Tadros, *Nature*, 1942, **150**, 22) 1-*bromo*-1 : 2-*diphenyl*-2-p-*methylthiophenylethylene* (II) and 1-*phenyl*-2 : 2-*bis*-p-*methylthiophenylethylene* (III) were prepared. (II) was found to be active in doses of 1 mg. but less active than its oxygen analogue, 1-bromo-1 : 2-diphenyl-2-*p*-methoxyphenylethylene (I). (III), given either subcutaneously or by stomach tube in 1 mg. doses, produced no oestrogenic effect (oestrogenic results reported by Dr. J. M. Robson, Department of Pharmacology, Guy's Hospital, London). (II) and (III) were prepared by a method similar to that used for (I) (Koelsch, *J. Amer. Chem. Soc.*, 1932, **54**, 2487).

(*b*) *Reduction of* p-*Methylthiobenzophenone* (IV) *and Bis*-p-*methylthiobenzophenone* (V).—When (IV) or (V) was treated with zinc dust in the presence of alcoholic potassium hydroxide, p-*methylthiobenzhydrol* (VI) or *bis*-p-*methylthiobenzhydrol* (VII) respectively was obtained (scheme A); on the other hand, when treated with zinc dust in the presence of acetic acid, s-*bis*-p-*methylthiobenzpinacol* (VIII) or s-*tetrakis*-p-*methylthiobenzpinacol* (IX) respectively was obtained (scheme B).



(*c*) *Photochemical Behaviour of the Pinacols* (VIII) *and* (IX).—Schönberg and Mustafa (*J.*, 1944, 67; *Chem. Reviews*, 1947, **40**, 182) were unable to reduce xanthone to the corresponding pinacol by the action of *iso*propyl alcohol in sunlight, in contrast to the ready formation of benzpinacol by the action of *iso*propyl alcohol on benzophenone in sunlight (Bachmann, *Org. Synth.*, 1934, **14**, 8). They also found that, in the case of xanthopinacol and fluorenopinacol, the reverse reaction takes place. Similarly I have found that when (VIII) and (IX) were exposed to sunlight in acetone solution, (IV) and (V) respectively were formed. (IV) and (V) are stable towards *iso*propyl alcohol in sunlight. The formation of the ketones (IV) and (V) is a true photochemical reaction, the pinacols (VIII) and (IX) being stable towards acetone in the dark.

For a possible mechanism of this reverse reaction see Schönberg and Mustafa (*loc. cit.*).

(*d*) *Reactions with Benzophenone Chloride and Bis*-p-*methylthiobenzophenone Chloride.*—When benzophenone is treated with thionyl chloride, benzophenone ketochloride is obtained. This gives (i) benzophenoneanil when treated with aniline (Pauly, *Annalen*, 1887, **187**, 199), (ii) tetraphenylethylene when refluxed with diphenylmethane (Norris, Thomas, and Brown, *Ber.*, 1910, **43**, 2958), and (iii) diphenyl ketazine when treated with hydrazine hydrate (Curtius and Rauterberg, *J. pr. Chem.*, 1891, **44**, 192).

Similarly, (V) forms the corresponding keto-chloride when treated with thionyl chloride and this, by the action of thioacetic acid, yields *bis*-p-*methylthiophenylthione* (X) (Schönberg, Schütz, and Nickel, *Ber.*, 1928, **61**, 1375):

$$>C{:}O \xrightarrow{SOCl_2} >C\!<\!\begin{matrix}Cl\\Cl\end{matrix} \xrightarrow{CH_3\cdot CO\cdot SH} >C\!<\!\begin{matrix}Cl\\SH\end{matrix} \longrightarrow >C{:}S + HCl$$

With solid mercuric chloride (X) in benzene shows the colour reaction described for diphenylthione derivatives (Schönberg, *Ber.*, 1925, **58**, 1793). (X) is transformed into s-*tetrakis*-p-*methylthiophenylethylene* (XI) when its solution in xylene is refluxed with copper bronze (Schönberg, Schütz, and Nickel, *loc. cit.*).

(*e*) *Reactions of* p-*Methylthiobenzophenone* (IV) *and Bis*-p-*methylthiobenzophenone* (V).—The ketone (IV) was converted into its *hydrazone* and *bis*-p-*methylthiophenyl ketazine*; (V) was converted into its anil and *bisphenylthiobis*-p-*methylthiophenylmethane*.

Experimental.

Action of Benzylmagnesium Chloride on p-*Methylthiobenzophenone* (IV).—The ketone (IV) (Schönberg, *Annalen*, 1924, **436**, 205) (10 g.) was treated with an ethereal solution of benzylmagnesium chloride [prepared from magnesium (1·4 g.), benzyl chloride (6·3 g.), and ether (75 c.c.)], and refluxed with stirring for 2 hours. The oil obtained after decomposition of the product with cold aqueous ammonium chloride was washed with light petroleum (b. p. 30—50°) and taken up in benzene from which it crystallised, after the addition of light petroleum (b. p. 30—50°), in colourless crystals, m. p. 117°. The yield was almost theoretical (Found: C, 78·5; H, 6·3; S, 10·1. $C_{21}H_{20}OS$ requires C, 78·8; H, 6·2; S, 10·0%). 2-*Hydroxy*-1 : 2-*diphenyl*-2-p-*methylthiophenylethane* was soluble in cold benzene and ethyl alcohol. It gave a deep red colour with concentrated sulphuric acid.

1-*Bromo*-1 : 2-*diphenyl*-2-p-*methylthiophenylethylene* (II).—This was prepared by adding a solution of the calculated amount of bromine in acetic acid to the hydroxy-ethane dissolved in the same solvent. The bromo-compound, which separated on cooling, recrystallised from absolute ethyl alcohol in colourless crystals, m. p. 105° (Found : C, 65·9; H, 4·4; Br, 21·5; S, 8·0. $C_{21}H_{17}BrS$ requires C, 66·1; H, 4·5; Br, 21·0; S, 8·4%). It gave a red-brown colour with sulphuric acid on standing.

2-Hydroxy-1 : 2-diphenyl-2-*p*-methylthiophenylethane was subjected to vacuum distillation in the presence of one drop of 20% sulphuric acid and gave an oily distillate which was easily soluble in alcohol, benzene, and light petroleum (b. p. 30—50°). This oily material when treated with bromine as described above gave (II), m. p. 105°, undepressed on admixture with a specimen prepared as above.

2-*Hydroxy*-1-*phenyl*-2 : 2-*bis*-p-*methylthiophenylethane*.—This was similarly prepared from bis-*p*-methylthiobenzophenone (V) (Schönberg, *loc. cit.*) (5 g.) and benzylmagnesium chloride [prepared from magnesium (0·7 g.), benzyl chloride (3·2 g.), and ether (40 c.c.)]. The *carbinol* crystallised from benzene after the addition of light petroleum (b.p. 30—50°) in colourless crystals, m. p. 118° (Found : C, 72·5; H, 6·1; S, 17·3. $C_{33}H_{32}OS_2$ requires C, 72·1; H, 6·0; S, 17·5%). It was soluble in benzene and hot ethyl alcohol, and gave a dark blue-green colour with sulphuric acid.

1-*Phenyl*-2 : 2-*bis*-p-*methylthiophenylethylene* (III).—2-Hydroxy-1-phenyl-2 : 2-bis-*p*-methylthiophenylethane (10 g.) was distilled in a vacuum in the presence of one drop of 20% sulphuric acid. The distillate was crystallised from light petroleum (b. p. 70—80°) yielding the *ethylene* in colourless crystals, m. p. 106° (Found : C, 75·9; H, 5·8; S, 18·2. $C_{33}H_{30}S_2$ requires C, 75·8; H, 5·7; S, 18·4%). It was soluble in benzene and ethyl alcohol, and difficultly soluble in light petroleum (b. p. 30—50°). The compound gave a dark blue-green colour with sulphuric acid.

Reduction of p-*Methylthiobenzophenone* (IV) *and Bis*-p-*methylthiobenzophenone* (V) *in Alkaline Medium*.—(i) p-*Methylthiobenzhydrol* (VI). The ketone (IV) (2 g.) was treated with zinc dust (4 g.) and alcoholic potassium hydroxide (2 g. in 20 c.c.) and refluxed for 45 minutes. The hot mixture was filtered and the filtrate treated with a few drops of water and cooled, giving the *benzhydrol* which crystallised from ethyl alcohol in colourless crystals, m. p. 99° (Found : C, 72·9; H, 6·1; S, 13·5. $C_{14}H_{14}OS$ requires C, 73·1; H, 6·1; S, 13·9%). (VI) was soluble in cold benzene and hot ethyl alcohol, and gave a red colour with sulphuric acid.

(ii) *Bis*-p-*methylthiobenzhydrol* (VII). The ketone (V) (2 g.) was reduced as described above in the case of (IV). *Bis*-p-*methylthiobenzhydrol* was obtained in colourless crystals from light petroleum (b. p. 70—80°), m. p. 98° (Found : C, 65·0; H, 5·9; S, 23·0. $C_{15}H_{16}OS_2$ requires C, 65·1; H, 5·8; S, 23·2%). It was easily soluble in benzene and hot ethyl alcohol and gave a malachite-green colour with sulphuric acid.

Reduction of p-*Methylthiobenzophenone* (IV) *and Bis*-p-*methylthiobenzophenone* (V) *in Acid Medium*.—(i) *s-Bis*-p-*methylthiobenzpinacol* (VIII). The ketone (IV) (1 g.) was dissolved in 80% ethyl alcohol (15 c.c.) and treated with zinc dust (3 g.) and glacial acetic acid (15 c.c.) (Cohen, *Rec. Trav. chim.*, 1919, **38**, 72, 113). The mixture was refluxed on the water bath for 2 hours, cooled and filtered and the solid residue washed with water, dried, and crystallised from benzene after the addition of light petroleum (b. p. 30—50°); colourless crystals, m. p. 175° (Found : C, 73·2; H, 5·7; S, 13·5. $C_{28}H_{26}O_2S_2$ requires C, 73·4; H, 5·7; S, 13·9%). The *benzpinacol* (VIII) was soluble in cold benzene and hot ethyl alcohol, and gave a malachite-green colour with sulphuric acid.

(ii) *s-Tetrakis*-p-*methylthiobenzpinacol* (IX). This was obtained by the reduction of (V) (1 g.) as described for (IV). The *benzpinacol* (IX) crystallised from benzene after the addition of light petroleum (b. p. 30—50°) in colourless crystals, m. p. 169° (Found : C, 65·2; H, 5·6; S, 22·9. $C_{30}H_{30}O_2S_4$ requires C, 65·4; H, 5·5; S, 23·3%). It was easily soluble in benzene, difficulty soluble in cold alcohol, and gave a violet colour with sulphuric acid.

Photochemical Action of Acetone on s-*Bis*-p-*methylthiobenzpinacol* (VIII).—(VIII) (2 g.) in acetone (25 c.c.) was exposed to sunlight for one month (May—June) in a sealed "Pyrex"-glass tube, from which the air had been displaced by dry carbon dioxide. The acetone was removed under reduced pressure and the solid residue of *p*-methylthiobenzophenone (IV) crystallised from benzene after the addition of light petroleum (b. p. 30—50°), m. p. and mixed m. p. 79°. The presence of *iso*propyl alcohol in the acetone solution was indicated by the formation of the *p*-nitrobenzoate (Schönberg and Mustafa, *J.*, 1943, 276).

Photochemical Action of Acetone on s-*Tetrakis*-p-*methylthiobenzpinacol* (IX).—The exposure of (IX) in acetone to sunlight for one month (May—June) gave bis-*p*-methylthiobenzophenone (V), m. p. and mixed m. p. 125°, and *iso*propyl alcohol.

Reactions of Bis-p-*methylthiobenzophenone* (V).—(i) *Bis*-p-*methylthiophenylthione* (X). Bis-*p*-methylthiobenzophenone chloride, prepared from (V) (4 g.) and thionyl chloride (30 c.c.) by heating under reflux, was dissolved in dry benzene (20 c.c.), thioacetic acid (5 c.c.) was added in a stream of dry carbon dioxide, and the mixture was refluxed for 6 hours, when a deep blue colour was observed. The excess of benzene and thioacetic acid was removed by distillation, and on addition of light petroleum (b. p. 30—50°) to the residue, *bis*-p-*methylthiophenylthione* (X) was deposited in blue crystals. It was recrystallised from benzene–light petroleum (b. p. 50—60°), m. p. 136° (blue melt) (Found : C, 61·9; H, 4·9; S, 32·9. $C_{15}H_{14}S_3$ requires C, 62·1; H, 4·8; S, 33·1%). It dissolved in hot benzene to a greenish-blue solution, was difficultly soluble in light petroleum (b. p. 30—50°), and very sparingly soluble in acetone. When mercuric chloride crystals were added to a dilute solution of the thione in benzene, they acquired a red-brown colour.

(ii) s-*Tetrakis*-p-*methylthiophenylethylene* (XI). (X) (2 g.), dissolved in xylene (30 c.c.), was refluxed with copper bronze (5 g.) for 8 hours. The hot xylene solution was filtered and concentrated; on cooling the *ethylene* (XI) separated in colourless crystals, recrystallised from benzene after the addition of light petroleum (b. p. 30—50°), m. p. 220° (Found : C, 70·0; H, 5·5; S, 24·6. $C_{30}H_{28}S_4$ requires C, 69·8; H, 5·4; S, 24·8%). It was soluble in hot benzene and difficultly soluble in alcohol.

(iii) *Bis*-p-*methylthiobenzophenoneanil*. This was obtained, from alcohol, in yellow crystals, m. p. 135° (identified by m. p. and mixed m. p.) (Schönberg, *loc. cit.*).

(iv) *Bisphenylthiobis*-p-*methylthiophenylmethane*. To a solution of the ketone (V) (1 g.) in the least

amount of hot glacial acetic acid (15 c.c.), thiophenol (1 g.), and anhydrous zinc chloride (a few sticks) were added. The reaction mixture was saturated with hydrogen chloride, and kept overnight at room temperature (cf. Baumann, *Ber.*, 1885, **18**, 888). It was poured into excess of water, extracted with ether, washed with dilute aqueous sodium hydroxide, and the ether evaporated leaving colourless crystals. The *methane* was recrystallised from light petroleum (b. p. 90—100°), m. p. 119° (Found: C, 68·2; H, 5·0; S, 26·6. $C_{27}H_{24}S_4$ requires C, 68·1; H, 5·0; S, 26·9%). It was easily soluble in cold benzene and hot alcohol, and gave a violet colour with sulphuric acid.

Reactions of p-*Methylthiobenzophenone* (IV).—p-*Methylthiobenzophenone hydrazone.* This was prepared by heating a mixture of hydrazine hydrate (1·8 g.), absolute ethyl alcohol (1 c.c.), and (IV) (5 g.) in a sealed tube at 160° for 6 hours (Curtius and Rauterberg, *loc. cit.*). p-*Methylthiobenzophenone hydrazone* was obtained from alcohol in colourless crystals, m. p. 95° (Found: C, 69·2; H, 5·6; N, 11·5; S, 13·0. $C_{14}H_{14}N_2S$ requires C, 69·4; H, 5·8; N, 11·6; S, 13·2%). It was easily soluble in hot alcohol and cold benzene.

Bis-p-*methylthiophenylketazine.* This was obtained by oxidation of *p*-methylthiophenylbenzophenone hydrazone by yellow mercuric oxide, as described for xanthone hydrazone (Schönberg and Stolpp, *Ber.*, 1930, **63**, 3114), in almost colourless crystals from light petroleum (b. p. 80—90°), m. p. 156—157° (Found: C, 74·2; H, 5·0; N, 6·1; S, 13·8. $C_{28}H_{24}N_2S_2$ requires C, 74·3; H, 5·3; N, 6·2; S, 14·1%). It was easily soluble in benzene and hot ethyl alcohol.

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83. *Experiments in the Chemistry of Benzthiazole.*

By WILLIAM A. BOGGUST and WESLEY COCKER.

A number of 6-substituted derivatives of benzthiazole have been prepared. It has been shown that some of these are smoothly degraded by hydrazine to *o*-aminothiophenols. When benzthiazole and phenylhydrazine are heated together they act as an oxidation–reduction system, the former being recovered unchanged, and the latter being converted into a mixture of benzene, aniline, ammonia, and nitrogen.

6-Aminobenzthiazole undergoes angular ring-closure in the Skraup reaction, with formation of *pyridino*(2′ : 3′ : 6 : 7)*benzthiazole*. *4′-Hydroxy-6′-methylpyridino*(2′ : 3′ : 6 : 7)*benzthiazole* is also obtained by the cyclisation of *ethyl β-*(*6-benzthiazolylamino*)*crotonate*.

SINCE a good supply of benzthiazole was available to one of us (Cocker, *J. Soc. Chem. Ind.*, 1936, **55**, 281T) an investigation of a number of its simple derivatives was undertaken. The starting point of our work was 6-nitrobenzthiazole which was prepared by a modification of the method described by Mylius (Diss., Berlin, 1883; Jacobsen and Kwaysser, *Annalen*, 1893, **277**, 244). The following benzthiazoles have been prepared: 6-amino-, 6-(p-*dimethylaminobenzylideneamino*)-, 6-(p-*acetamidobenzenesulphonamido*)-, 6-(p-*aminobenzenesulphonamido*)-, 6-*hydroxy*-, 6-*chloro*-, 6-*bromo*-, 6-*cyano*-, 6-*carboxy*-, 6-*carbomethoxy*-, 6-*hydrazino*-, and 6-*carbamido*-. 6-Aminobenzthiazole was prepared by reduction of the nitro-compound with stannous chloride (Mylius, *loc. cit.*), activated iron powder (Clemo and Legg, *J.*, 1947, 544), or ferrous sulphate and ammonia (cf. Friedländer, *Ber.*, 1882, **15**, 2573). 6-Aminobenzthiazole was converted into its *p*-acetamidobenzenesulphonamido-derivative without difficulty, and this compound, and the *p*-aminobenzenesulphonamido-derivative, were examined for inhibitory action against various micro-organisms. Both compounds exhibited inhibitory properties against *Gonococcus* and hæmolytic *Streptococcus*, but both were less effective than sulphanilamide. The low activity was, however, possibly due to the sparingly soluble nature of both compounds in the culture media. Furthermore, both were found to possess relatively high toxicity when tested against mice.

When 6-aminobenzthiazole was diazotised in hydrochloric acid and the diazonium solution was decomposed with copper sulphate and sulphuric acid, 6-chlorobenzthiazole, and not the expected phenol, was obtained. Treatment of the chloro-compound with 3 : 5-dinitrobenzoyl chloride gave 5-chloro-2-(3 : 5-dinitrobenzamido)thiophenol with cleavage of the thiazole ring.

This ring-cleavage is interesting in that benzthiazole derivatives are known to undergo oxidation to the corresponding 2 : 2′-dibenzthiazolyls on treatment with benzoyl chloride (Hofmann, *Ber.*, 1880, **13**, 1229), and we have shown that stearoyl chloride effects this change. On the other hand, a mixture of benzoyl chloride and alkali has been used for opening the thiazole ring (see Morton " The Chemistry of Heterocyclic Compounds ", New York, 1946, p. 408, for numerous references).

The replacement of the diazonium group by chlorine in the presence of cupric salts is known (cf. Hodgson, Birtwell, and Walker, *J.*, 1941, 772), and it appears that such replacements are prevalent with diazonium ions of high positivity. In the case under discussion, the electron-attractive characteristics of the $-N{=}\overset{|}{C}-S-$ group are probably responsible for the reaction mentioned.

Formation of the true phenol proceeded normally by decomposition of the diazonium sulphate.

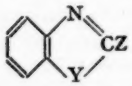
The 6-chloro-, -bromo-, and, -cyano-compounds were also obtained in the normal way by using the appropriate cuprous salt, but attempts to obtain the 6-iodo-compound gave a semi-solid material which decomposed explosively. This was probably due to the formation of a periodide.

An attempt to obtain benzthiazole-6-hydrazide by the reaction of hydrazine with 6-carbomethoxybenzthiazole yielded 2 : 2′-*diamino*-5 : 5′-*dicarbomethoxydiphenyl disulphide*.

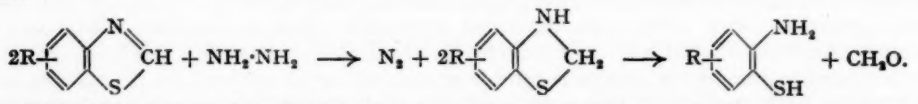
Under the same conditions, benzthiazole yielded 2 : 2′-diaminodiphenyl disulphide ("Intramine") in good yield, and likewise 6-cyanobenzthiazole yielded 2 : 2′-*diamino*-5 : 5′-*dicyanodiphenyl disulphide*. 5 : 5′-Dinitro-2 : 2′-diaminodiphenyl disulphide was similarly obtained from 6-nitrobenzthiazole, and the pyridino(2 : 3′ : 6 : 7)benzthiazole described later yielded 6 : 6′-*diamino*-5 : 5′-*diquinolyl disulphide*. Hydrolysis of the thiazole ring takes place in all these reactions.

A number of methods are known for the opening of thiazole and similar five-membered heterocyclic rings. Thus benzthiazole is hydrolysed to *o*-aminothiophenol by concentrated sodium hydroxide at elevated temperatures (Hofmann, *Ber.*, 1880, **13**, 18), although more recently (B.P. 558,887) it has been shown that less drastic conditions can be employed. Reductive cleavage is quite common. Thus sodium in alcohol has been used for this purpose (Schatzmann, *Annalen*, 1891, **261**, 6; Schuftan, *Ber.*, 1894, **27**, 1009), but so far as we are aware, the use of hydrazine under mild conditions such as those described is new. A somewhat similar reaction involves the formation of 2-formamidophenol when benzoxazole is treated with hydroxylamine, but 2-aminobenzoxazole is simultaneously produced (Skraup, *Annalen*, 1919, **419**, 68).

It was at first thought that either 2-aminobenzthiazole or 2-hydrazinobenzthiazole would be possible intermediates in the formation of the disulphide. The former compound was obtained by amination of benzthiazole with hydroxylamine (Skraup, *loc. cit.*), and the latter was obtained from 2-mercaptobenzthiazole by treatment with hydrazine. The latter preparation follows the work described in the patent literature (D.R.-P. 614,327) in which it is stated that compounds of the type (I) when treated with hydrazine give 2-substituted hydrazino-compounds. However,

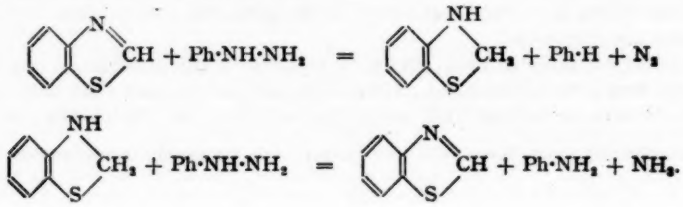
(I.)  (Y = S, O, NH, N·Alk; Z = OH, Cl, SO_3H.)

neither 2-amino- nor 2-hydrazino-benzthiazole suffered ring-cleavage on further heating with hydrazine. In view of the fact that cleavage of thiazole systems by alkaline reducing agents is known (*loc. cit.*), it is considered probable that the benzthiazole is first reduced to the corresponding thiazoline which is then hydrolysed to an aminothiophenol and formaldehyde or some derivative of this, the thiophenol being oxidised in the subsequent manipulation. In agreement with this view is the fact that an inert gas, probably nitrogen, is evolved during the reaction :



Formaldehyde was never detected during the reaction, but the aqueous liquors from which the amino-thiol or the amino-disulphide separated yielded a hygroscopic non-sulphur-containing nitrogenous solid which yielded a benzylidene derivative. Neither compound has been identified.

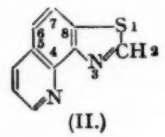
Piperidine, dimethylaniline, and alkaline sodium hydrosulphite (dithionite) did not hydrolyse benzthiazole, but when benzthiazole was heated with phenylhydrazine it was recovered almost quantitatively, whereas the phenylhydrazine was converted into a mixture of nitrogen, ammonia, benzene, and aniline in amounts corresponding to the requirements of the equations below, in which there is an oxidation–reduction system.

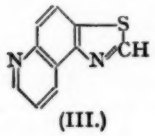


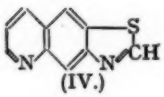
The equations given above conform with the known facts about the oxidising and reducing properties of phenylhydrazine. It is also known that benzthiazolines are very readily oxidised even in air (Lankelma and Sharnhoff, *J. Amer. Chem. Soc.*, 1931, **53**, 2654). Small amounts of aniline and ammonia were evolved when phenylhydrazine was refluxed for extended periods, but the amounts obtained were not comparable to those mentioned above, and benzene was not identified.

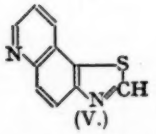
In view of the physiological activity of many thiazole compounds, and of the importance of the quinoline nucleus in many compounds of chemotherapeutic value, it was considered worth while to prepare compounds of the quinthiazole type. Some such compounds are known and have been prepared by the Skraup reaction. Thus Erlenmeyer and Ueberwasser (*Helv. Chim. Acta*, 1940, **23**, 328) described the preparation of pyridino(2′ : 3′ : 4 : 5)benzthiazole (II).

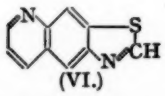
The mode of preparation leaves the identity of this quinthiazole in no doubt, but the application of the Skraup reaction to 5-aminobenzthiazole, obtained from 2-chloro-5-nitroformanilide *via* 5-nitrobenzthiazole (D.R.-P. 442,773), could lead to either pyridino(3′ : 2′ : 4 : 5)-benzthiazole (III) by angular ring-closure or pyridino(2′ : 3′ : 5 : 6)benzthiazole (IV) by linear ring-closure. 6-Aminobenzthiazole can similarly yield either a linear or an angular quinthiazole.

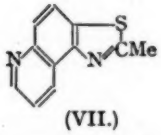

(II.)


(III.)


(IV.)

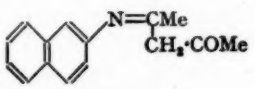

(V.)

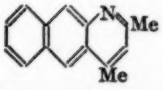

(VI.)


(VII.)

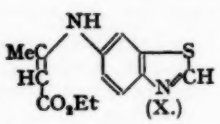
6-Aminobenzthiazole readily undergoes the Skraup reaction when sodium *m*-nitrobenzenesulphonate is used as the oxidising agent. This reaction could give either pyridino(2′ : 3′ : 6 : 7)-benzthiazole (V) or pyridino(3′ : 2′ : 5 : 6)benzthiazole (VI). All the evidence goes to show, however, that the former compound is actually obtained.

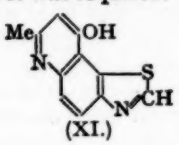
Although as a rule, angular systems are formed in preference to linear systems (cf. Kermack and Weatherhead, *J.*, 1940, 1164), the linear system cannot entirely be ruled out. Thus Cohen *et al.* (*J.*, 1934, 656) obtained 5-chloro-2 : 4-dimethyl-1-aza-anthracene by the ring closure of 4-(5-chloro-2-naphthylimino)pentan-2-one and Clemo and Legg (*J.*, 1945, 830) obtained 2 : 4-dimethyl-6 : 7-benzoquinoline (IX) by the cyclisation of 4-(2-naphthylimino)pentan-2-one (VIII).

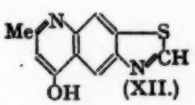
(VIII.) 


(IX.)

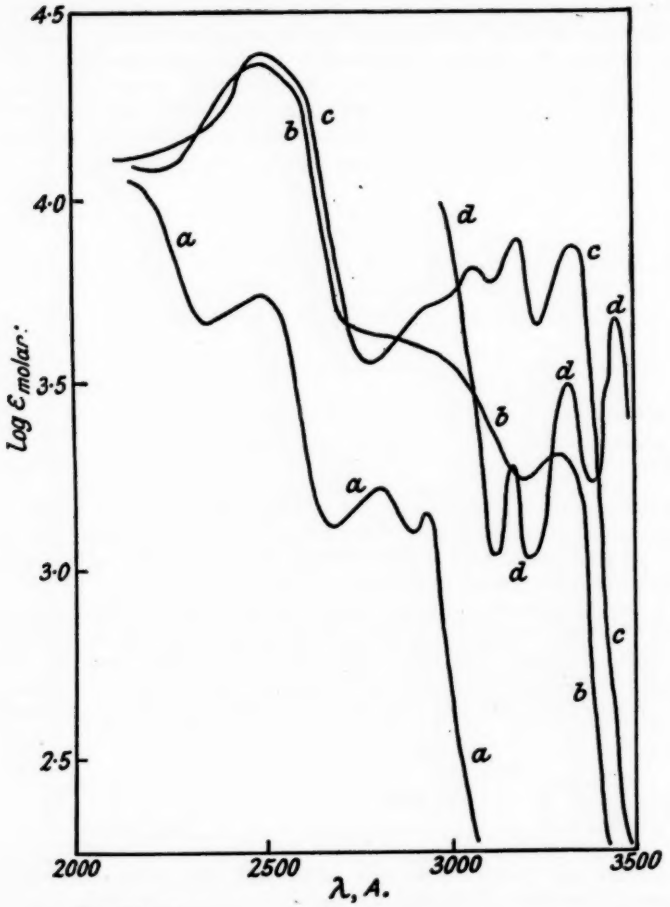
According to Fries and Wolter (*Annalen*, 1936, **527**, 60) benthiazole occupies a position intermediate between benzoid and naphthoid reactivity, although these authors state that the Skraup reaction with 5-amino-2-methylbenzthiazole leads to the production of 2-methyl pyridino(3′ : 2′ : 4 : 5)benzthiazole (VII). Ochiai and Nisizawa (*Ber.*, 1941, **74**, *B*, 1407) showed that the allyl ether of 6-hydroxy-2-methylbenzthiazole rearranges to give a mixture of 6-hydroxy-2-methyl-7- and -5-allylbenthiazoles in which the former is present in the ratio of 20 to 1. This evidence and that of Fries and Wolter give strong support for the acceptance of the angular form (V) for the quinthiazole now described rather than the linear form (VI). It would also appear likely that the angular structure (XI) would also arise from the cyclisation of the crotonate (X). In view, however, of the work of Cohen *et al.* (*loc. cit.*) and Clemo and Legg (*loc. cit.*), proof of the suggested structures was required.


(X.)


(XI.)


(XII.)

6-Aminobenzthiazole and ethyl acetoacetate were condensed at 28° for 5 days; the product was *ethyl* β-(6-*benzthiazolylamino*)*crotonate* since water was rapidly produced when the reactants were first mixed. There is very considerable evidence that at low temperatures this mode of condensation takes place in preference to that which would lead to the formation of 6-acetoacetamidobenzthiazole, a reaction which proceeds on the water-bath (cf. Conrad and Limpach, *Ber.*, 1887, **20**, 944; 1888, **21**, 523, 1649; 1891, **24**, 2990; Stark, *Ber.*, 1907, **40**, 3431; Knorr, *Annalen*, 1886, **236**, 112; *Ber.*, 1892, **25**, 772; Coffey, Thompson, and Wilson, *J.*, 1936, 856; Hazlewood, Hughes, and Lyons, *J. Proc. Roy. Soc. N.S.W.*, 1937, **71**, 472). The crotonate was



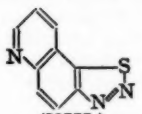
a. *Benzthiazole.*
b. *Pyridino*(2′ : 3′ : 6 : 7)*benzthiazole* (V).
c. 4′-*Hydroxy*-6′-*methylpyridino*(2′ : 3′ : 6 : 7)*benzthiazole* (XI).
(*All in alcohol.*)
d. 3-*Chloro*-2 : 4-*dimethyl*-5 : 6-*benzoquinoline* (*Clemo and Legg*).

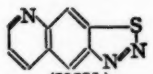
cyclised by addition to high-boiling paraffin preheated to 270°, a method successfully used for similar cyclisations by Hazlewood, Hughes, and Lyons (*loc. cit.*), and assuming that the cyclisation took place to give an angular structure, 4′-*hydroxy*-6′-*methylpyridino*(2′ : 3′ : 6 : 7)*benzthiazole* (XI) would be the expected product. Spectroscopic evidence shows that this compound and the quinthiazole (V) have similar structures, and it is most likely that they have the angular structures assigned to them. On the other hand cyclisation to give a linear ring system would have led to the production of 4′-hydroxy-6′-methylpyridino(3′ : 2′ : 5 : 6)benthiazole (XII).

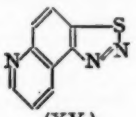
In order to establish the structure of the unsubstituted quinthiazole, oxidation to the corresponding quinone by means of chromic oxide in acetic acid was attempted. A quinthiazole of the angular type (V) should yield an orthoquinone capable of detection by quinoxaline

formation, whereas the linear compound (VI) should yield a paraquinone (cf. Clemo and Legg, *loc. cit.*). Unfortunately, however, the quinthiazole was, in every case, recovered unchanged. Quinthiazole failed to condense with maleic anhydride.

In view of the ready cleavage of the thiazole ring with hydrazine, attempts were made to utilise this method to distinguish between the two possible quinthiazoles (V) and (VI), since the former should give 6-amino-5-mercaptoquinoline whilst the latter should yield 6-amino-7-mercaptoquinoline (or the corresponding disulphides) on treatment with hydrazine. The removal of the amino-group from the product of the hydrolysis would then lead to the production of either 5- or 7-mercaptoquinoline. Unfortunately, however, whilst the thiazole was hydrolysed to the corresponding aminoquinoline disulphide, diazotisation of this compound yielded the not unexpected thiadiazole which could be either (XIII) or (XIV) (cf. Jacobsen, *Ber.*, 1888, **21**, 3105; Jannsen, *Annalen*, 1893, **277**, 219). A similar compound, pyridino(3′ : 2′ : 4 : 5)benzthiadiazole (XV), was prepared by Fries and Reitz (*Annalen*, 1936, **527**, 38) by the Skraup


(XIII.)


(XIV.)


(XV.)

reaction on 5-aminothiadiazole and its angular structure was justified on the grounds that 4-chloro-5-aminothiadiazole failed to undergo the Skraup reaction. In view of the fact that the new quinthiazole (V) most likely has an angular structure, the thiadiazole prepared from it is probably *pyridino*(2′ : 3′ : 6 : 7)*benzthiadiazole* (XIII).

Thiadiazoles usually decompose when heated above their melting points, yielding thianthrenes (Jacobsen and Ney, *Ber.*, 1889, **22**, 910), but when the thiadiazole (XIII) was heated above its melting point, although decomposition apparently took place, the thiadiazole was either recovered unchanged or a charred mass was produced from which it was impossible to isolate any crystalline product.

Examination of the ultra-violet light absorption of (V) and (XI) lends some support to the probability that these compounds have angular structures. The fig. shows that the ring system in these compounds is essentially the same, and making due allowance for the extra ring in the compounds mentioned the absorption is very similar to that of benzthiazole. The maximum at 2500 A. in each case may be due to the thiazole ring. In thiazole itself the maximum is located at 2400 A., and there is also a similar maximum in anthracene, phenanthrene, and pyridine (Braude, *Ann. Reports*, 1945, 105) to which the thiazoles are somewhat similar in aromaticity. Further, the curves for compounds (V) and (XI) shown in the fig. show a resemblance to those of 2 : 4-dimethyl- and 3-chloro-2 : 4-dimethyl-5 : 6-benzoquinoline (Clemo and Legg, *loc. cit.*) where angular structures are involved, but they are very different from the curves obtained by these authors for 2 : 4-dimethyl-6 : 7-benzoquinoline and other aza-anthracenes. The maxima shown by the quinthiazoles bear the approximate relationship to those shown by benzthiazole that those of phenanthrene do to those of naphthalene (cf. Braude, *loc. cit.*). On the other hand the anthracenes and aza-anthracenes have maxima at higher wave-lengths than the corresponding angular structures.

When 6-aminobenzthiazole was brominated, a mixture of monobromo-compounds was obtained from which pure compounds, m. p. 119—120° and 145—146°, were isolated. The lower-melting compound yielded the quinthiazole (V) with bromine elimination when subjected to the Skraup reaction, and this bromo-compound was probably *7-bromo-6-aminobenzthiazole*. In view of the work of Ochiai and Nisizawa it is likely that the other bromo-compound was 5-bromo-6-aminobenzthiazole, but when it was subjected to the Skraup reaction it yielded a high-melting bromo-compound which did not give correct analyses for the expected 5-bromopyridino(2′ : 3′ : 6 : 7)benzthiazole.

Experimental.

(Microanalyses and ultra-violet light-absorption data are by Drs. Weiler and Strauss, Oxford.)

Benzthiazole, prepared from triply recrystallised sulphate, gave the following maxima in the ultra-violet: 2500 A. (log ϵ 3·74), 2840 A. (log ϵ 3·22), and 2960 A. (log ϵ 3·15).

6-Nitrobenzthiazole.—Crude benzthiazole obtained as described by Cocker (*loc. cit.*) was first purified by a double vacuum distillation. It was then converted into its sulphate which after crystallisation from alcohol was decomposed by alkali. The benzthiazole was distilled and collected at 125—128°/18 mm. Benzthiazole (33 g.) was slowly added with stirring to concentrated sulphuric acid (66 c.c.) at 10—20°. Nitric acid (33 c.c., *d* 1·42) was then added dropwise at 5—10°. Stirring was

continued for a further hour, the temperature being allowed to rise to 20°, and the mixture was poured on ice. The solid product was washed with water, yielding a mixture of nitro-compounds (25 g., m. p. 140—145°). This mixture was purified by extraction with a deficiency of methyl alcohol which left the 6-nitrobenzthiazole undissolved. The required compound was obtained as a pale yellow solid (9·6 g.), m. p. 171—173°. This was considered pure enough for further work, but a pure specimen was obtained, by crystallisation from a large volume of alcohol, as pale yellow needles, m. p. 174° (Mylius, *loc. cit.*).

6-*Aminobenzthiazole.*—(*a*) The nitro-compound (1·0 g.), dissolved in a mixture of methyl alcohol (10·0 c.c.), concentrated hydrochloric acid (10·0 c.c.), and stannous chloride (5·0 g.), was heated under reflux for 15 minutes. The methyl alcohol was then distilled off, and the residue was dissolved in water and strongly basified to remove tin salts. Extraction of the mixture with ether yielded a solid which, after distillation in a vacuum (b. p. 184°/2 mm.), yielded the required amine (0·8 g.), m. p. 81—82°. Crystallisation from benzene–light petroleum yielded long colourless needles, m. p. 84—85° (Mylius, *loc. cit.*, gives m. p. 87°).

(*b*) The nitro-compound (7·5 g.) in alcohol (100 c.c.) was added to etched iron filings (45 g.), and the mixture was refluxed for 3 hours and filtered, and the alcohol removed, leaving the amine (5·3 g.), m. p. 79—82°.

(*c*) The nitro-compound (1 g.), suspended in a solution of ferrous sulphate (18 g.) in water (30 c.c.) containing hydrochloric acid (2 drops), was shaken at 90° with ammonia (*d* 0·88), added in 1 portion of 3·5 c.c. and 3 further portions of 1·25 c.c. After cooling, the sludge was repeatedly extracted with ether, from which the required amine (0·5—0·6 g.) was obtained, m. p. 82—83°. Its p-*dimethylaminobenzylidene* derivative crystallised from alcohol in yellow plates, m. p. 135° (Found : C, 68·05; H, 5·6. $C_{16}H_{15}N_3S$ requires C, 68·3; H, 5·3%).

6-(p-*Acetamidobenzenesulphonamido*)*benzthiazole.*—A mixture of 6-aminobenzthiazole (0·3 g.), *p*-acetamidobenzenesulphonyl chloride (0·5 g.), and acetone (5·0 c.c.) was treated with pyridine (2·0 c.c.). The mixture was warmed to give a clear solution, and left overnight at room temperature. It was then poured into water, yielding a solid (0·6 g.) which after crystallisation from alcohol was obtained as silvery prisms, m. p. 253—254° (decomp.) (Found : C, 51·6; H, 4·0. $C_{15}H_{13}O_3N_3S_2$ requires C, 51·8; H, 3·8%). 6-(p-*Aminobenzenesulphonamido*)*benzthiazole* was obtained by warming this *acetyl* derivative (1·0 g.) on the water-bath with concentrated hydrochloric acid (5·0 c.c.) and water (2·0 c.c.) for 30 minutes. The mixture was basified with sodium carbonate, yielding a solid, which crystallised from alcohol as colourless prisms, m. p. 210·5° (Found : C, 51·2; H, 3·6. $C_{13}H_{11}O_2N_3S_2$ requires C, 51·1; H, 3·6%).

6-*Carbamidobenzthiazole.*—A solution of 6-aminobenzthiazole hydrochloride (1 g.) in water (10 c.c.) was treated with potassium cyanate (1 g.), and the mixture was heated on the water-bath for 15 minutes. The precipititate was washed and dried, yielding the *carbamido*-compound as a white solid (0·6 g.) which crystallised from aqueous methyl alcohol as silvery prisms, m. p. 194° (Found : C, 49·4; H, 3·7. $C_8H_7ON_3S$ requires C, 49·7; H, 3·6%).

6-*Chlorobenzthiazole.*—(*a*) A solution of 6-aminobenzthiazole (1·0 g.) in concentrated hydrochloric acid (2·0 c.c.) and water (5·0 c.c.) was diazotised at 0° with sodium nitrite (0·5 g.) in water (1·0 c.c.). After 30 minutes, the solution was slowly added to a boiling mixture of copper sulphate (10 g.), sulphuric acid (70 g.), and water (40 c.c.). After cooling, the mixture was diluted to 500 c.c. and extracted with chloroform, from which the *chloro*-compound was obtained as an oil (0·5 g.), b. p. 111°/2 mm. It rapidly solidified and was sublimed in a vacuum giving colourless needles, m. p. 41° (Found : C, 49·5; H, 2·4. C_7H_4NClS requires C, 49·6; H, 2·4%). Its *picrate* crystallised from alcohol as bright yellow needles, m. p. 136° (Found : C, 39·4; H, 1·8. $C_{13}H_7O_7N_4ClS$ requires C, 39·15; H, 1·7%). 5-*Chloro*-2-(3 : 5-*dinitrobenzamido*)*thiophenol* was obtained when 6-chlorobenzthiazole was heated gently with an equivalent quantity of 3 : 5-dinitrobenzoyl chloride. It was soluble in sodium hydroxide, and crystallised from dilute alcohol as colourless needles, m. p. 154° (Found : C, 44·4, 44·3; H, 2·35, 2·1. $C_{13}H_6O_5N_3ClS$ requires C, 44·2; H, 2·3%).

(*b*) 6-Aminobenzthiazole (1·0 g.), diazotised in sulphuric acid (1·5 c.c.) and water (3·0 c.c.) with sodium nitrite (0·44 g.), was added to cuprous chloride (0·3 g.) in hydrochloric acid (3·0 c.c.). After 12 hours the mixture was diluted, basified with ammonia, and extracted with ether, yielding the chloro-compound which sublimed as needles (0·6 g.), m. p. 40°.

6-*Bromobenzthiazole.*—6-Aminobenzthiazole (1·0 g.) was diazotised in hydrobromic acid (6·0 c.c., *d* 1·4) and added to a stirred ice-cold solution of cuprous bromide (1·1 g.) in hydrochloric acid (15 c.c.). The mixture was warmed on the water-bath to complete the reaction, cooled, basified with excess of ammonia, and extracted with ether, from which the *bromo*-compound was obtained as an oil (0·85 g.), b. p. 143°/1—2 mm. This quickly solidified; it sublimed in a vacuum as colourless needles, m. p. 55° (Found : C, 40·0; H, 1·9. C_7H_4NBrS requires C, 39·25; H, 1·8%).

6-*Cyanobenzthiazole.*—6-Aminobenzthiazole (2·0 g.) diazotised in hydrochloric acid was added to a warm (40—50°) solution of sodium cuprocyanide prepared from hydrated copper sulphate (3·7 g.) and sodium cyanide (3·3 g.). After 30 minutes on the water-bath, further sodium cyanide was added to decompose the copper complex, and the solution was extracted with ether, from which the *cyano*-compound (1·1 g.) was obtained. It was sublimed in a vacuum, and then crystallised from benzene–light petroleum as long colourless needles, m. p. 138° (Found : C, 59·6; H, 2·8. $C_8H_4N_2S$ requires C, 60·0; H, 2·5%).

Benzthiazole-6-carboxylic Acid.—The *cyano*-compound (0·2 g.) was refluxed for 1 hour with a mixture of concentrated sulphuric acid (4·5 c.c.) and water (3·0 c.c.). This mixture was diluted, basified with sodium carbonate, filtered, and acidified with dilute acetic acid. The precipitated *acid* was collected (0·2 g.) and crystallised from dilute alcohol (charcoal) as colourless needles, m. p. 245—246° (Found : C, 54·0; H, 3·3. $C_8H_5O_2NS$ requires C, 53·6; H, 2·8%). Its *methyl* ester crystallised from dilute methyl alcohol as silvery flakes, m. p. 106—107° (Found : C, 56·4; H, 3·4. $C_9H_7O_2NS$ requires C, 56·0; H, 3·6%). Its *anilide* crystallised from alcohol as glistening plates, m. p. 176° (Found : C, 65·6; H, 3·9. $C_{14}H_{10}ON_2S$ requires C, 66·1; H, 3·9%).

6-*Hydroxybenzthiazole.*—6-Aminobenzthiazole (5·6 g.) dissolved in a solution of sulphuric acid (6·5 c.c.) in water (11·0 c.c.) was diazotised at 0—5° with sodium nitrite (1·6 g.) in water (7·0 c.c.).

After 15 minutes, the solution was added to a boiling solution of sulphuric acid (19 c.c.) in water (94 c.c.). When cool, the mixture was basified with ammonia and extracted with ether, from which the *hydroxy*-compound was obtained (1·5 g.). After sublimation in a vacuum, it crystallised from ethyl acetate–light petroleum as colourless prisms, soluble in sodium hydroxide, m. p. 181—182° (Found: C, 55·25; H, 3·3. C_7H_5ONS requires C, 55·6; H, 3·3%). Its *picrate* crystallised from water as orange-yellow prisms, m. p. 194—195° (Found: C, 42·1; H, 2·5. $C_{13}H_8O_8N_4S$ requires C, 41·1; H, 2·1%).

6-*Hydrazinobenzthiazole*.—6-Aminobenzthiazole (4·0 g.), diazotised in hydrochloric acid, was slowly added to a solution of stannous chloride (14 g.) in concentrated hydrochloric acid (14 c.c.). The mixture was warmed for several minutes, cooled, basified with sodium hydroxide, and extracted with chloroform, from which a solid (3·8 g.), m. p. 93°, was obtained. After 3 crystallisations from benzene (charcoal), the *hydrazine* was obtained as colourless needles, m. p. 101—102° (Found: C, 51·3; H, 4·2. $C_7H_7N_3S$ requires C, 50·9; H, 4·2%).

Pyridino(2′ : 3′ : 6 : 7)*benzthiazole* (V).—6-Aminobenzthiazole (1·0 g.) was mixed to a paste with glycerol (3·0 c.c.) and heated to 110°. A mixture of sodium *m*-nitrobenzenesulphonate (4 g.) and 78% sulphuric acid (12 g.) was then added during 30 minutes, and the mixture was heated at 110° for 12 hours. It was cooled, diluted, and extracted with benzene, from which colourless glistening needles (0·6 g.), m. p. 158—159°, were obtained. The *quinthiazole* was finally crystallised from light petroleum (b. p. 80—100°); m. p. 159—160° (Found: C, 64·0; H, 3·3. $C_{10}H_6N_2S$ requires C, 64·5; H, 3·2%). The ultra-violet light-absorption of this compound in absolute alcohol showed maxima at 2500 A. (log ε 4·35) and 3320 A. (log ε 3·31). Its *monomethiodide* crystallised from methyl alcohol as orange needles, m. p. 270—271° (Found: I, 38·6. $C_{11}H_9N_2IS$ requires I, 38·7%). Its *picrate* crystallised from boiling xylene in greenish-yellow rosettes, m. p. 238—239° (Found: C, 46·9; H, 2·6. $C_{16}H_9O_7N_5S$ requires C, 46·3; H, 2·2%).

Ethyl β-(6-*Benzthiazolylamino*)*crotonate* (X).—A mixture of 6-aminobenzthiazole (5 g.), freshly distilled ethyl acetoacetate (4 g.), and concentrated hydrochloric acid (1 drop) was left for 4 days at 28°. Water was quickly produced on mixing the reactants, and this was finally removed by dissolving the mixture in ether and drying the solution (Na_2SO_4). The solution was concentrated under reduced pressure to 10 c.c., and the residue then deposited the desired *compound* (6·5 g.) as colourless tablets, m. p. 62°. Crystallisation from light petroleum (b. p. 40—60°)–benzene raised the m. p. to 63° (Found: C, 59·8; H, 5·0. $C_{13}H_{14}O_2N_2S$ requires C, 59·5; H, 5·3%).

4′-*Hydroxy*-6′-*methylpyridino*(2′ : 3′ : 6 : 7)*benzthiazole* (XI).—The above crotonate (2·2 g.) was finely powdered and added to liquid paraffin (30 c.c.) preheated to 270°. The mixture was heated for a further 10 minutes and cooled, and the solid (1·6 g.) was collected and washed with light petroleum. After 2 crystallisations from dilute alcohol, the required *compound* was obtained as colourless micro-needles, m. p. 360—361° (decomp.) (Found: C, 60·5; H, 3·6. $C_{11}H_8ON_2S$ requires C, 61·1; H, 3·7%). The ultra-violet light-absorption of this compound in alcohol showed maxima at 2500 A. (log ε 4·38), 3080 A. (log ε 3·81), 3200 A. (log ε 3·89), and 3380 A. (log ε 3·88).

4′-*Chloro*-6′-*methylpyridino*(2′ : 3′ : 6 : 7)*benzthiazole*.—The hydroxy-compound (0·5 g.) was heated for 1 hour under reflux with phosphorus oxychloride (10 c.c.), and the excess of oxychloride was then removed under reduced pressure. After being triturated with ether, the residue solidified. It was collected, washed with more ether, and ground with ammonia. The free *base* was collected, washed with water, and dried. Two crystallisations from alcohol yielded colourless needles (0·3 g.), m. p. 153° (Found: C, 56·4; H, 3·2. $C_{11}H_7N_2ClS$ requires C, 56·3; H, 3·0%). Attempts to condense this compound with 4-amino-1-diethylaminopentane were unsuccessful.

2 : 2′-*Diamino*-5 : 5′-*dicarbomethoxydiphenyl Disulphide*.—Methyl benzthiazole-6-carboxylate (0·7 g.) was refluxed in methyl alcohol (5 c.c.) with hydrazine hydrate (100% : 1·5 c.c.) for 3 hours and left overnight at room temperature. The deposited *disulphide* (0·5 g.) was collected and crystallised from methyl alcohol as brilliant yellow needles insoluble in sodium hydroxide; m. p. 193—194° (Found: C, 52·4; H, 4·3. $C_{18}H_{16}O_4N_4S_2$ requires C, 52·7; H, 4·5).

5 : 5′-*Dinitro*-2 : 2′-*diaminodiphenyl Disulphide*.—6-Nitrobenzthiazole (0·5 g.) was refluxed in absolute alcohol (3 c.c.) with hydrazine hydrate (100% : 1·0 c.c.) for 3 hours. Alcohol was removed under reduced pressure, and the residue was treated with water and filtered. The filtrate was made just acid with hydrochloric acid, and the yellow solid was collected (0·4 g.). On crystallisation from alcohol, the disulphide was obtained as yellow needles insoluble in sodium hydroxide; m. p. 222° (cf. Mylius, *loc. cit.*, who gives m. p. 237°) (Found: C, 42·6; H, 3·0. Calc. for $C_{12}H_{10}O_4N_4S_2$: C, 42·6; H, 3·0%).

2 : 2′-*Diamino*-5 : 5′-*dicyanodiphenyl Disulphide*.—6-Cyanobenzthiazole (0·65 g.), refluxed for 3 hours with hydrazine hydrate (100%, 1·3 c.c.) in absolute alcohol (3·0 c.c.), yielded a low-melting solid on cooling. After dilution with water, the solution was aspirated for several hours, and the precipitated product was collected. Two crystallisations from dilute alcohol gave the *disulphide* as yellow prisms, m. p. 188° (Found: C, 55·5; H, 3·9. $C_{14}H_{10}N_4S_2$ requires C, 56·3; H, 3·4%).

6 : 6′-*Diamino*-5 : 5′-*diquinolyl Disulphide*.—Pyridino(2′ : 3′ : 6 : 7)benzthiazole (V) (0·5 g.), refluxed for 3 hours with hydrazine hydrate (100%; 1 c.c.) in alcohol (3·0 c.c.), yielded an intensely orange solution from which, by operations as described above, an orange powder (0·4 g.) was obtained. This *disulphide* crystallised from alcohol as dark orange prisms, insoluble in sodium hydroxide, m. p. 240° (Found: C, 61·7; H, 4·2. $C_{18}H_{14}N_4S_2$ requires C, 61·7; H, 4·0%).

Pyridino(2′ : 3′ : 6 : 7)*benzthiadiazole* (XIII).—The disulphide (0·6 g.), in N-hydrochloric acid (10·5 c.c.), was diazotised with sodium nitrite (0·3 g.). This solution was added to boiling alcohol (50 c.c.) containing zinc dust (0·5 g.). After boiling for 15 minutes longer the alcohol was removed, and the residue was diluted with water and basified with ammonia, yielding a yellow solid (0·35 g.), m. p. 172°. The *thiadiazole* was crystallised twice from alcohol, and so obtained as very pale yellow needles, m. p. 182° (Found: C, 58·3; H, 3·0. $C_9H_5N_3S$ requires C, 57·7; H, 2·7%). It decomposed when heated above its m. p., and, on refluxing with zinc dust and mineral acid followed by basification, it yielded ammonia.

2 : 2′-*Diaminodiphenyl Disulphide* (" *Intramine* ").—Benzthiazole (10 g.), refluxed for 3 hours with hydrazine hydrate (100%; 20 c.c.) in alcohol (20 c.c.), and the alcohol removed, yielded after treatment

with hydrogen peroxide (100-vol.; 1·5 c.c.), a bright yellow solid (8·5 g.) which crystallised from dilute alcohol as lustrous yellow plates, m. p. 92° (Hofmann, *Ber.*, 1897, **12**, 2359, gives m. p. 93°) (Found: C, 57·6; H, 4·8. Calc. for $C_{12}H_{12}N_2S_2$: C, 58·0; H, 4·8%).

2-Hydrazinobenzthiazole.—2-Mercaptobenzthiazole (0·5 g.) was refluxed in alcohol (3·5 c.c.) with hydrazine hydrate (100%; 2 c.c.) for 3 hours. Ammonia and hydrogen sulphide were evolved, and on cooling, 2-hydrazinobenzthiazole was obtained which crystallised from dilute alcohol as yellow needles, m. p. 199·5° (D.R.-P. 614,327, *loc. cit.*) (Found: C, 51·3; H, 4·2. Calc. for $C_7H_7N_3S$: C, 51·0; H, 4·2%). The same compound was obtained when 2 : 2′-dibenzthiazolyl disulphide was similarly treated with hydrazine hydrate.

Attempted Formation of Pyridino(2′ : 3′ : 6 : 7)benzthiazole–Maleic Anhydride Adduct.—The quinthiazole (V) (0·2 g.), maleic anhydride (0·5 g.), and dry benzene (5·0 c.c.) were refluxed for 6 hours. After filtration from a little solid, hydrogen chloride was passed in, and a hydrochloride, m. p. 246—247°, was collected. This was refluxed in acetone with sodium acetate, the liquid filtered, and the residual sodium acetate extracted with several portions of boiling acetone. From the combined extracts, the original quinthiazole (0·15 g.), m. p. 158°, was recovered.

Reaction of Phenylhydrazine and Benzthiazole.—Benzthiazole (3·0 g.) was heated under reflux with varying amounts of freshly distilled phenylhydrazine for 6 hours. A vigorous reaction set in immediately on heating, and the ammonia evolved was collected in excess of N/10-sulphuric acid. The residual liquid in the reaction flask was distilled, and the benzene collected at 75—80° and characterised as nitrobenzene. The higher-boiling liquid was then dissolved in ether and extracted with 3 portions each of 5 c.c. of 10% hydrochloric acid. The ethereal layer was washed with water, dried (Na_2SO_4), and fractionated to yield benzthiazole, b. p. 225—230°. Its picrate had m. p. 167—168° undepressed by authentic benzthiazole picrate. The acid extract was basified and extracted with ether, from which aniline, b. p. 179—184°, and phenylhydrazine, b. p. 240—245°, were obtained by fractionation. The aniline was characterised as acetanilide and the phenylhydrazine as its benzylidene derivative.

Bromination of 6-Aminobenzthiazole.—A mixture of 6-aminobenzthiazole (0·5 g.), anhydrous sodium acetate (0·5 g.), and chloroform (0·5 c.c.) was cooled to 0°, and a solution of bromine (0·5 c.c.) in chloroform (5·0 c.c.) was slowly added. After 15 minutes, the solid was collected, and triturated with a solution of sodium hydrogen sulphite, then with a solution of sodium carbonate, and finally with water. The dried solid (0·3 g.) had m. p. 138°. After sublimation in a vacuum and crystallisation from dilute alcohol, a *monobromo*-compound was obtained as colourless needles, m. p. 145—146° (Found: C, 36·9; H, 2·2. $C_7H_5N_2BrS$ requires C, 36·7; H, 2·2%).

In the absence of sodium acetate, another bromination yielded a crude product (0·1 g.), m. p. 95°. Repeated crystallisation from dilute alcohol yielded *7-bromo-6-aminobenzthiazole* as glistening needles, m. p. 119—120° (Found: C, 36·2; H, 2·3%). Bromination in acetic acid in absence of sodium acetate yielded an orange solid, m. p. 230°, which on being washed with sodium hydrogen sulphite and water yielded a mixture of the two bromo-compounds. From the acetic acid mother liquors, the higher-melting bromo-compound was obtained in pure condition. When 7-bromo-6-aminobenzthiazole (1 g.) was heated at 110° with 70% sulphuric acid (12 g.), sodium *m*-nitrobenzenesulphonate (4 g.), and glycerol (3 c.c.) for 12 hours, and the product isolated by basification and extraction with benzene, pyridino-(2′ : 3′ : 6 : 7)benzthiazole, m. p. 158—159° was obtained. When the higher-melting bromo-compound was treated under similar conditions, a new *bromo*-compound was obtained which crystallised from alcohol as needles, m. p. 223° (Found: C, 37·9; H, 2·0%). This has not been identified.

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[*Received, March 30th*, 1948.]

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84. *Reaction-kinetic Investigations of the Incomplete Dissociation of Salts. Part I. The Decomposition of Diacetone Alcohol in Solutions of Metallic Hydroxides.*

By R. P. BELL and J. E. PRUE.

It is shown that measurements of reaction velocities may provide a useful method for estimating the degree of dissociation of salts in solution. Data are given for the rate of decomposition of diacetone alcohol in solutions of sodium, potassium, rubidium, calcium, barium, and thallous hydroxides. Values derived for the dissociation constants of the species $CaOH^+$, $BaOH^+$, and TlOH are in fair agreement with values obtained from other sources. It is concluded that the formation of $CaOH^+$ and $BaOH^+$ can be reasonably accounted for on electrostatic grounds, but that TlOH must involve covalent binding.

THE interionic attraction theory gives a satisfactory account of the thermodynamic behaviour of very dilute salt solutions, but the physical and mathematical approximations employed break down as the concentration increases, especially for small ions. Attempts have been made to carry the mathematical approximations of the Debye–Hückel theory a stage further (Gronwall, *Proc. Nat. Acad. Sci.*, 1927, **13**, 198; Gronwall, LaMer, and Sandved, *Physikal. Z.*, 1928, **29**, 358), but these lead to inconsistencies which show that the physical bases of the treatment are too crude to warrant such refinement (cf., *e.g.*, Guggenheim and Fowler, "Statistical Thermodynamics", p. 407, Cambridge, 1939). An analysis of the experimental data shows

(Brönsted, *J. Amer. Chem. Soc.*, 1922, **44**, 877; Guggenheim, *Phil. Mag.*, 1935, **19**, 588) that the individual deviations of electrolytes from the simple Debye–Hückel theory depend essentially on the short-range interactions between pairs of ions of opposite charge. Part of these deviations can be described by supposing that a certain fraction of the electrolyte is undissociated, and behaves like a non-electrolyte (or, in the case of an unsymmetrical electrolyte, like an ion of reduced charge), while the free ions obey the simple Debye–Hückel law. This idea was first introduced by Bjerrum (*Kgl. Danske Vid. Selsk. Mat.-fys. Medd.*, 1926, **7**, No. 9) and shown to account successfully for the activity coefficients and conductivities of many electrolytes, and his treatment was further developed by Fuoss (*Trans. Faraday Soc.*, 1934, **30**, 967). These authors treated ionic association as a purely electrostatic phenomenon, but it has been shown by Davies (*e.g.*, *J.*, 1938, 276; 1939, 349, and earlier papers) that consistent values for the dissociation constants of many " strong " electrolytes can be derived from experimental data without making assumptions about the nature of the forces involved.

In deriving these values it is necessary to ascribe to incomplete dissociation all deviations from ideal or standard behaviour, and considerable difficulty arises in the choice of such standards for different properties of electrolyte solutions. There has therefore been some difference of opinion as to the status of the dissociation constants obtained : for example, they have been described as having " more of the nature of an adjustable mathematical parameter than a definite physical entity " (Owen and Gurry, *J. Amer. Chem Soc.*, 1938, **60**, 3074). This view might be justified if the concept of incomplete dissociation were successful only in accounting for thermodynamic properties. However, it has been shown by Davies (*loc. cit.*) that the same dissociation constants will also account for the conductivity data, and in some cases yet other properties of salt solutions (*e.g.*, optical rotation). It is the purpose of the present series of papers to investigate how far the velocities of reactions involving salts can be similarly interpreted in terms of incomplete dissociation.

When an ion of a strong electrolyte takes part in a reaction with a neutral molecule (either as a reactant or as a catalyst) the reaction velocity is usually more closely proportional to the concentration of the ion than to its activity (cf. Bell, " Acid–Base Catalysis ", p. 13, Oxford, 1941). This suggests that, when the ion is present as a salt which is incompletely dissociated, the reaction velocity may be used as a measure of its true concentration. The problem can be expressed more precisely in terms of the transition-state theory of reaction velocity. If an ion X^-, present as a salt XY, is reacting with an uncharged molecule S, the reaction velocity expression will contain the stoicheiometric concentrations of X^- and S, multiplied by an activity coefficient factor $f_S f_{X^-}/f_{XS^-}$, where XS^- is the transition state. In fairly dilute solutions f_S will be effectively unity, and, since X^- and XS^- have the same charge, f_{X^-}/f_{XS^-} will also be close to unity in the absence of any specific interaction between Y^+ and X^- or XS^- : hence in this case the reaction velocity will be directly proportional to the stoicheiometric concentration of X^-, as is found in many cases. If, on the other hand, either X^- or XS^- or both interact specifically with Y^+, the term f_{X^-}/f_{XS^-} must be retained. In particular, if X^- interacts specifically with Y^+ but XS^- does not (*e.g.*, if XSY is completely dissociated and XY is not), then the reaction-velocity expression will contain a factor representing only the specific part of the interaction between X^- and Y^+. The kinetic method should thus lead to the same degrees of dissociation as other methods provided that we can neglect the association of the transition state XS^- with any oppositely charged ions. This is likely to be the case, since the transition state will always be larger than the ion X^-, and its charge is often spread over several atoms, but it cannot be assumed without experiment. For catalytic reactions the statement that Y^+ does not interact specifically with the transition state is equivalent to saying that there is no catalysis by the species XY, so that the most suitable reactions for the present purpose are likely to be those which exhibit specific catalysis by hydrogen or hydroxyl ions rather than general acid–base catalysis.

The reaction studied in the present paper is the depolymerisation of diacetone alcohol, which has long been known as an instance of specific hydroxyl-ion catalysis (Koelichen, *Z. physikal. Chem.*, 1900, **33**, 129; Akerlöf, *J. Amer. Chem. Soc.*, 1926, **48**, 3046; 1927, **49**, 2955; 1928, **50**, 1279; LaMer and Miller, *ibid.*, 1935, **57**, 2674). Previous investigators have shown that in solutions of sodium and potassium hydroxides the reaction velocity is directly proportional to the stoicheiometric hydroxyl-ion concentration up to about 0·1N, but that barium hydroxide gives velocities as much as 7% lower (Koelichen, *loc. cit.*). Since Davies has derived a value of about 0·2 for the dissociation constant $[Ba^{++}][OH^-]/[BaOH^+]$, this difference is of the expected order of magnitude. A similar effect would be expected for calcium hydroxide, and we have also investigated thallium hydroxide, for which Ostwald (*J. pr. Chem.*, 1887, **35**, 114) found a

conductivity–concentration curve differing considerably from those of the alkali-metal hydroxides, suggesting incomplete dissociation.

There is some difference of opinion as to the kinetic mechanism of the diacetone alcohol depolymerisation. The more probable scheme is that suggested by Hammett (" Physical Organic Chemistry ", p. 344, New York 1940), *i.e.* :

$$CH_3{\cdot}CO{\cdot}CH_2{\cdot}CMe_2{\cdot}OH + OH^- \rightleftharpoons CH_3{\cdot}CO{\cdot}CH_2{\cdot}CMe_2{\cdot}O^- + H_2O \quad \text{(fast)}$$

$$CH_3{\cdot}CO{\cdot}CH_2{\cdot}CMe_2{\cdot}O^- \longrightarrow [CH_3{\cdot}CO{\cdot}CH_2]^- + COMe_2 \quad \text{(slow)}$$

$$[CH_3{\cdot}CO{\cdot}CH_2]^- + H_2O \longrightarrow COMe_2 + OH^- \quad \text{(fast)}$$

On the other hand, Butler and Nelson (*J.*, 1938, 957) have suggested the following alternative mechanism on the basis of the hydrogen isotope effect :

$$CH_3{\cdot}CO{\cdot}CH_2{\cdot}CMe_2{\cdot}OH + OH^- \longrightarrow CH_3{\cdot}CO{\cdot}CH_2{\cdot}\underset{CH_2^-}{CMe{\cdot}OH} + H_2O \quad \text{(slow)}$$

$$\left.\begin{aligned} CH_3{\cdot}CO{\cdot}CH_2{\cdot}\underset{CH_2^-}{CMe{\cdot}OH} &\longrightarrow [CH_3{\cdot}CO{\cdot}CH_2]^- + CH_2{:}C(OH){\cdot}CH_3 \\ CH_2{:}C(OH){\cdot}CH_3 &\longrightarrow CH_3{\cdot}CO{\cdot}CH_3 \\ [CH_3{\cdot}CO{\cdot}CH_2]^- + H_2O &\longrightarrow CH_3{\cdot}CO{\cdot}CH_3 + OH^- \end{aligned}\right\} \text{(fast)}$$

For our present purpose the distinction between the two mechanisms is not an important one, since in each of them the transition state is a large organic species bearing one negative charge.

Experimental.

Diacetone alcohol was obtained by redistilling a commercial preparation under 30 mm. pressure, and was stored in hard-glass vessels. It contained not more than 4×10^{-4} mole of free acid per 100 g.

Table I.

(c = concentration in g.-equiv./l.)

Sodium hydroxide.

c(NaOH) ...	0·01046	0·02093	0·02616	0·03139	0·04186	0·05005	0·05181	0·0751	0·1001
$10^3k/[OH^-]$ *	218·0	216·7	217·9	218·0	216·7	217·0	217·3	216·1	214·6
c(NaOH) ...	0·1335	0·1668	0·2002	0·2336	0·2669	0·3003	0·3337	0·3671	0·4002
$10^3k/[OH^-]$ *	212·7	211·6	211·1	210·3	209·0	207·8	207·1	205·6	205·1

cNaOH + ½cNaCl.

c(NaOH)	0·0508	0·1016	0·1524	0·2002	0·2708	0·3337	0·3809
$10^3k/[OH^-]$ *	214·0	211·8	207·7	205·6	203·8	200·8	200·3

Potassium hydroxide. cKOH + ½cKCl.

c(KOH) ...	0·1633	0·2449	0·3266	0·3592	0·3918	0·0816	0·1633	0·2612	0·3102	0·3674
$10^3k/[OH^-]$ *	216·8	217·6	216·5	216·6	217·7	215·7	213·7	210·6	210·8	209·0

Rubidium hydroxide. cRbOH + ½cRbCl.

c(RbOH)	0·0674	0·1679	0·2686	0·3021	0·3324	0·1007	0·2014	0·3021
$10^3k/[OH^-]$ * ...	217·8	218·5	219·3	218·9	218·7	215·6	213·9	212·8

Calcium hydroxide.

c[Ca(OH)$_2$]	0·01442	0·01802	0·02162	0·02523	0·02882	0·03243	0·03569
$10^3k/[OH^-]$ *	203·8	201·9	202·1	197·3	197·3	193·4	194·2

0·025NaOH + cCaCl$_2$ + (0·175 − 3c/2)NaCl.

(Ionic strength = 0·2 throughout.)

c(CaCl$_2$)	0	0·0200	0·0400	0·0700	0·0900
$10^3k/[OH^-]$ *	200·0	191·3	184·1	173·2	168·5

Barium hydroxide.

c[Ba(OH)$_2$]	0·04605	0·07402	0·09870	0·1316	0·1645	0·1974
$10^3k/[OH^-]$ *	208·4	204·3	197·5	194·5	190·3	185·5
c[Ba(OH)$_2$]	0·2303	0·2632	0·2961	0·3290	0·3619	0·3948
$10^3k[OH^-]$ *	184·5	182·7	179·7	178·7	176·3	173·8

Thallous hydroxide.

c(TlOH)	0·02050	0·04099	0·08882	0·1298	0·1708	0·2186	0·2665	0·3075	0·3383
$10^3k/[OH^-]$ * ...	212·1	204·2	192·1	185·0	175·8	169·4	165·1	162·7	158·1

Since the kinetic experiments were carried out with approximately 1% solutions, this amount of acid would cause an error of less than 0·5% in the most dilute solutions of alkali employed. Solutions of sodium, potassium, calcium, and barium hydroxides were prepared from the pure solids. Solutions of the hydroxides of thallium and rubidium were prepared by treating solutions of thallous sulphate and rubidium chromate respectively with a very slight excess of barium hydroxide solution. All hydroxide solutions were standardised against constant-boiling hydrochloric acid, and conductivity water was used throughout, strict precautions being taken to exclude carbon dioxide.

The kinetic measurements were made at 25° ± 0·01° in a simple dilatometer of about 25 c.c. capacity with a capillary 0·5 mm. in diameter. In order to prevent the formation of air bubbles, the hydroxide solutions were evacuated for a few minutes before use. After ten minutes in the thermostat the diacetone alcohol was added from a small automatic pipette, and the dilatometer filled by suction. Reliable readings could be obtained 8 minutes after mixing. The reactions were throughout strictly of the first order, and the velocity constants were calculated by the method of Guggenheim (*Phil. Mag.*, 1926, **7**, 538), their accuracy being estimated as about ±0·5%.

Results.—Table I gives values of the apparent catalytic constants $k/[OH^-]^*$ where k is the first-order velocity constant in terms of decadic logarithms and minutes, and $[OH^-]^*$ is the stoicheiometric concentration of hydroxyl ions in moles per litre, complete dissociation of the metallic hydroxides being assumed. Some measurements were carried out with mixtures of the type cNaOH + ½cNaCl in order to obtain data for comparison with $Ba(OH)_2$ solutions of the same $[OH^-]^*$ and the same ionic strength.

Discussion.

(a) *Alkali Hydroxides.*—Fig. 1 shows a plot of the observed catalytic constant $k/[OH^-]^*$ against the stoicheiometric hydroxyl-ion concentration for the hydroxides of sodium, potassium,

Fig. 1.

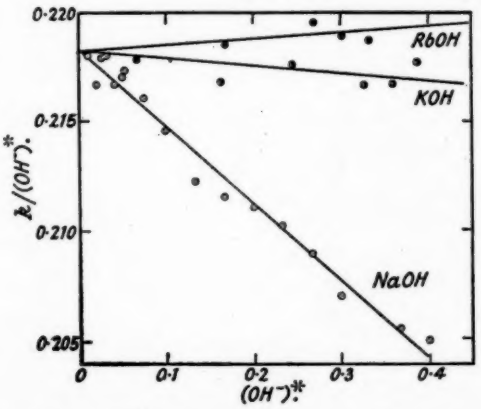
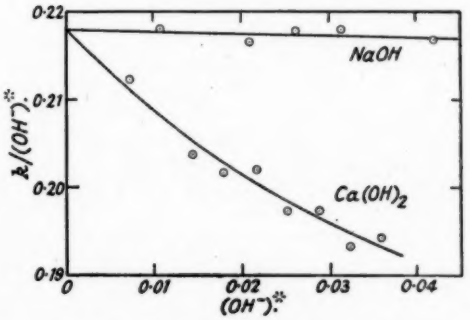


Fig. 2.



and rubidium. It will be seen that they all converge to the same value at infinite dilution, namely $0{\cdot}218_2$. This value is higher than those obtained by most previous workers (*e.g.*, French, *J. Amer. Chem. Soc.*, 1929, **51**, 3215; Murphy, *ibid.*, 1931, **53**, 977; Sturtevant, *ibid.*, 1937, **59**, 1534), but slightly lower than the value $0{\cdot}221_8$ given by LaMer and Miller (*loc. cit.*). These authors attribute values lower than their own to contamination by carbon dioxide or to impurities in the diacetone alcohol used, but this does not seem a likely explanation in our case in view of the good reproducibility with different samples of alkali and diacetone alcohol.

At higher concentrations potassium and rubidium hydroxides show respectively a slight decrease and a slight increase in catalytic constant, but this is barely greater than the experimental error of about 0·5%. On the other hand, sodium hydroxide shows a marked decrease in catalytic effect with increasing concentration, amounting to about 7% in 0·4N-solution. The same effect has been found by Akerlöf at higher concentrations, and analogous differences occur in the activity coefficients. Thus the tables compiled by Harned and Robinson (*Chem. Reviews*, 1941, **28**, 419) show that the mean activity coefficients of potassium and cæsium hydroxides are closely similar up to about 0·5N, while sodium hydroxide gives values up to 8% lower: similarly, indicator measurements by Schwarzenbach and Sulzberger (*Helv. Chim. Acta*, 1944, **27**, 348) indicate that concentrated solutions of potassium hydroxide are more strongly alkaline than corresponding solutions of sodium hydroxide. Both the kinetic and the thermodynamic data could be formally accounted for by supposing that sodium hydroxide differs from the other alkali hydroxides in being incompletely dissociated, but the dissociation constant involved would be so large (*ca.* 5) that it is doubtful whether this interpretation is a useful one. For present purposes we shall only conclude that at higher

concentrations potassium and rubidium hydroxides provide a better standard of "normal behaviour" than does sodium hydroxide.

(b) *Calcium Hydroxide.*—The catalytic constants for this hydroxide are plotted against $[OH^-]^*$ in Fig. 2, together with those for sodium hydroxide for comparison. (In the relevant concentration range there is no appreciable variation of $k/[OH^-]^*$ for any of the alkali hydroxides, so that it is immaterial which of them is used for comparison.) Both curves extrapolate to the same point at infinite dilution, but at the highest concentration the catalytic effect of the calcium hydroxide solutions has decreased by about 12%. The data given by Davies (*loc. cit.*) for the dissociation constant of $CaOH^+$ and its variation with ionic strength indicate a deficiency of 12·6% in the concentration of hydroxyl ions in this solution. It therefore seems likely that the kinetic results can also be accounted for on the basis of incomplete dissociation.

If we assume that the true hydroxyl-ion concentration is given by $[OH^-] = k/0{\cdot}2182$, we can obtain $[CaOH^+] = [OH^-]^* - [OH^-]$, and hence the concentration dissociation constant $K_c = [Ca^{++}][OH^-]/[CaOH^+]$. These values are given in the first columns of Table II.

TABLE II.

Calcium hydroxide.

$[OH^-]^*$.	$[OH^-]$.	$[CaOH^+]$.	$[Ca]^{++}$.	K_c.	I.	K_d'.
0·01442	0·01347	0·00095	0·00626	0·095	0·0197	0·050
0·01802	0·01668	0·00134	0·00767	0·101	0·0244	0·052
0·02162	0·02006	0·00156	0·00925	0·122	0·0293	0·059
0·02523	0·02282	0·00241	0·01020	0·102	0·0330	0·047
0·02882	0·02607	0·00275	0·01166	0·116	0·0377	0·052
0·03243	0·02874	0·00369	0·01253	0·102	0·0413	0·044
0·03569	0·03176	0·00393	0·01392	0·117	0·0457	0·050
					Mean K_d' =	0·051

The thermodynamic dissociation constant K_d differs from K_c by the inclusion of the activity coefficient factor $f_{Ca^{++}} f_{OH^-}/f_{CaOH^+}$. (The values for $f_{Ca^{++}}$ and f_{OH^-} are here of course the "true" rather than the stoicheiometric values: *i.e.*, they apply only to the unassociated ions Ca^{++} and OH^-.) In the absence of data for these activity coefficients we have used the standard expression suggested by Guggenheim (*Phil. Mag.*, 1935, **19**, 588) for the activity coefficient of a z-valent ion at an ionic strength I, *viz.*,

$$-\log_{10} f_z = 0{\cdot}5z^2 I^{\frac{1}{2}}/(1 + I^{\frac{1}{2}}) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

We can then define an approximate thermodynamic constant K_d' by

$$\log_{10} K_d' = \log_{10} K_c - 2I^{\frac{1}{2}}/(1 + I^{\frac{1}{2}}) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

and the values of this constant are given in the last column of Table II. They show no trend with concentration, and the deviations of individual values are not greater than would arise from an error of $\pm 0{\cdot}5\%$ in the kinetic measurements. It is therefore likely that the mean value of 0·051 is close to the true thermodynamic constant K_d, and this view is supported by the data given in Table I for mixtures of NaOH, NaCl, and $CaCl_2$. In these experiments the ionic strength was 0·2 throughout, and we have therefore taken as the standard catalytic constant the value for 0·025N-NaOH + 0·175N-NaCl, *i.e.*, $0{\cdot}200_0$. The true concentrations of hydroxyl ions are then calculated from $[OH^-] = k/0{\cdot}200$, and the remainder of the calculation is as before. The resulting values of K_d' are 0·047, 0·051, 0·049, 0·053; mean = 0·050. The excellent agreement with the former result is probably fortuitous in view of the uncertainty as to the correct value to take for the standard catalytic constant in these solutions.

The only other experimental data on the dissociation constant of $CaOH^+$ are those of Kilde (*Z. anorg. Chem.*, 1934, **218**, 118) on the effect of alkali on the solubility of calcium iodate. These data refer to ionic strengths of $I = 0{\cdot}05$—$0{\cdot}15$, and Kilde used an expression of the form (3)

$$-\log_{10} f_z = 0{\cdot}5z^2 I^{\frac{1}{2}} + BI \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

for extrapolating to zero ionic strength, obtaining $K_d = 0{\cdot}040$. Davies (*loc. cit.*) recalculated Kilde's results, introducing a correction for the incomplete dissociation of $CaIO_3^+$ and KIO_3, and used (4) for the activity coefficients. In this way he obtained $K_d = 0{\cdot}030$. The dissociation

$$-\log_{10} f_z = 0{\cdot}5z^2\{I^{\frac{1}{2}}/(1 + I^{\frac{1}{2}}) + BI\} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

constants of both these authors involve a large extrapolation, and hence depend considerably on the values adopted for the parameter B. It is therefore uncertain whether the differences between their values and our own value of 0·051 are significant. It should, however, be pointed

out that the kinetic method will yield too high values for the degree of dissociation if there is some association between the transition state and the calcium ion, and this might account for the somewhat higher value which we have obtained.

(c) *Barium Hydroxide.*—The catalytic constants for this hydroxide are shown in Fig. 3. In treating these data two difficulties arise which were not present for calcium hydroxide. In the first place, since the stoicheiometric hydroxyl-ion concentrations extend up to 0·4N, there is some latitude in the choice of standard catalytic constants for calculating the true concentrations of hydroxyl ions. We have made calculations on two different assumptions: (i) That the true catalytic constant is throughout $0{\cdot}218_2$, *i.e.*, the value applicable to all hydroxides in very dilute solution. (ii) That the true catalytic constant of the hydroxyl ion in a barium hydroxide solution is the same as the observed constant in a mixture of KOH + KCl having the same stoicheiometric hydroxyl-ion concentration and the same ionic strength.

The hydroxyl-ion concentrations calculated from these two assumptions are given in cols. 2 and 3 of Table III, and cols. 4 and 5 give the corresponding values of $K_c = [Ba^{++}][OH^-]/[BaOH^+]$. The data for the most dilute solution in Table I have been omitted from Table III, since the degree of association is very small and liable to considerable error. Both assumptions lead to a reasonably consistent set of values for K_c, with some tendency to increase with increasing ionic strength. However, the value of K_d must be considerably lower than those of K_c, since the lowest ionic strength concerned is about 0·1, and it is difficult to make correct allowance for the ionic activity coefficients in such concentrated solutions. Equation (1) will not be valid, but an expression like (4) is likely to apply at least to the more dilute solutions. We have therefore plotted $\log_{10}K_d$, [as defined by (2)] against I, and made a linear extrapolation to $I = 0$. The resulting plot is shown in Fig. 4, the vertical lines representing the error which would result from an error of $\pm 0{\cdot}5\%$ in the kinetic measurements. The linear extrapolations give $K_d = 0{\cdot}21$ and $K_d = 0{\cdot}24$ for assumptions (i) and (ii) respectively.

FIG. 3.

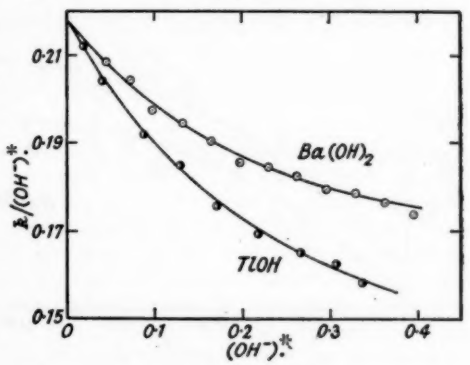


TABLE III.

Barium hydroxide.

	[OH⁻].		K_c.		$-\log_{10}K_d'$.		I.	
[OH⁻].*	(i.)	(ii).	(i).	(ii).	(i).	(ii).	(i).	(ii).
0·0740	0·0688	0·0696	0·42	0·40	0·855	0·776	0·101	0·102
0·0987	0·0894	0·0906	0·38	0·46	0·947	0·871	0·129	0·132
0·1316	0·1173	0·1193	0·42	0·52	0·957	0·872	0·169	0·173
0·1645	0·1434	0·1442	0·42	0·49	1·004	0·920	0·205	0·210
0·1974	0·1677	0·1715	0·39	0·48	1·055	0·979	0·227	0·244
0·2303	0·1947	0·1997	0·44	0·55	1·049	0·951	0·274	0·285
0·2632	0·2204	0·2268	0·43	0·59	1·055	0·951	0·309	0·322
0·2961	0·2438	0·2516	0·47	0·59	1·087	0·979	0·340	0·355
0·3290	0·2695	0·2787	0·45	0·60	1·082	0·970	0·375	0·393
0·3619	0·2923	0·3050	0·47	0·63	1·107	0·994	0·404	0·425
0·3948	0·3130	0·3251	0·44	0·59	1·145	1·029	0·429	0·453

These values may be compared with $K_d = 0{\cdot}23$ derived by Davies (*loc. cit.*) from the activity coefficient data of Harned and Masson (*J. Amer. Chem. Soc.*, 1932, **54**, 1441). The differences between the three values are not greater than the experimental and theoretical uncertainties of both methods. Davies's method for deriving degrees of association involves the assumption that all other interionic forces can be satisfactorily represented by equation (4), giving B the universal value $-0{\cdot}20$. The slopes of our extrapolations in Fig. 4 correspond to a much greater value of B (*ca.* $-0{\cdot}8$), and values of K_c calculated by Davies's method indicate a value of B considerably greater than $-0{\cdot}2$ if the data at higher concentrations are included. If a higher value of B were used throughout in Davies's calculations this would bring his values of K_c at higher concentrations into closer agreement with our own, but would not appreciably affect the extrapolated value of K_d.

(d) *Thallous Hydroxide.*—The plot of catalytic constant against $[OH^-]^*$ is given in Fig. 3. This hydroxide is of the same charge type as potassium and rubidium hydroxides, and since the latter deviate inappreciably from the limiting value $k/[OH^-]^* = 0{\cdot}218_2$ in the relevant concentration range, we have used this value in calculating the true values of $[OH^-]$ in Table IV. The values of K_c obtained are again reasonably consistent. In extrapolating to obtain K_d we have used K_d' as defined by equation (2) with the omission of the factor 2. Fig. 5 shows a plot of $-\log_{10}K_d'$ against I, with vertical lines corresponding again to $\pm 0{\cdot}5\%$ in the kinetic measurements. The extrapolated value corresponds to $K_d = 0{\cdot}38$.

The only other data for comparison with this value are Ostwald's conductivity measurements (*loc. cit.*). Since the mobilities of the ions Tl^+ and K^+ are almost identical, it is a reasonable assumption to take $\Lambda(TlOH)/\Lambda(KOH)$ at equal ionic concentrations as equal to the degree of dissociation of TlOH. Values of $-\log_{10}K_d'$ calculated on this assumption are plotted in Fig. 5, and agree fairly well with those derived from the kinetic data, though if taken alone they suggest a somewhat lower value of K_d, *ca.* 0·32.

FIG. 4.

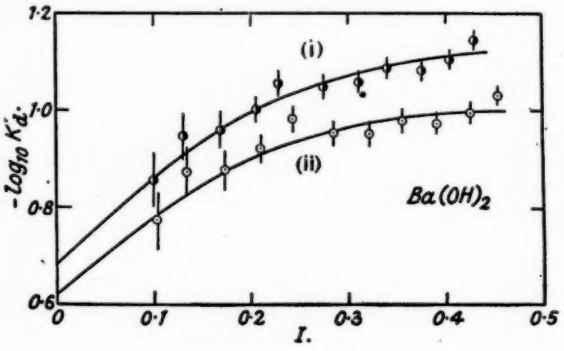


FIG. 5.

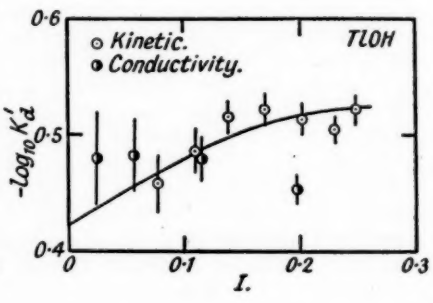


TABLE IV.

Thallous hydroxide.

$[OH^-]$.*	$[OH^-] = [Tl^+] = I$.	K_c.	$-\log_{10}K_d'$.	$[OH^-]$.*	$[OH^-] = [Tl^+] = I$.	K_c.	$-\log_{10}K_d'$.
0·0888	0·0782	0·59	0·459	0·2186	0·1697	0·60	0·522
0·1298	0·1092	0·58	0·486	0·2665	0·2017	0·63	0·512
0·1708	0·1376	0·57	0·515	0·3075	0·2292	0·67	0·503
0·2186	0·1697	0·60	0·522	0·3383	0·2452	0·63	0·521

General Conclusions.—The above data show that the kinetic method gives values for the degree of association of several metallic hydroxides which are in reasonable agreement with values derived by other methods. This justifies the assumption underlying the kinetic method, that the transition state in our reaction does not associate appreciably with the metallic ions present. It is of course by no means established that the same conclusion will hold good for other reactions or other solvents. For example, Schattenstein (*Acta Physicochim. U.R.S.S.*, 1935, **3**, 37; *J. Amer. Chem. Soc.*, 1937, **59**, 432) has studied the ammonolysis of santonin in liquid ammonia by a number of ammonium salts, and finds that the stoicheiometric catalytic constant of the ammonium ion varies only between the limits 0·0386—0·0492, although the degree of dissociation of the salts (as judged by their conductivities) varied from 4% to 47%. It appears that in this reaction the association of the ammonium ion with various anions is closely paralleled by the association of the transition state with the same ions. It is intended to investigate other reactions in aqueous solution from the same point of view.

The most probable values for K_d derived above are $CaOH^+$ 0·051, $BaOH^+$ 0·23, TlOH 0·38. From a practical point of view it may be noted that for the range of ionic strengths which we have used the degrees of dissociation are well represented by the mean concentration dissociation constants K_c, as follows, $CaOH^+$ 0·11, $BaOH^+$ 0·43, TlOH 0·60. From a theoretical point of view it is of interest to see how far the observed constants can be accounted for by Coulomb forces between the constituent ions. By applying Bjerrum's treatment (*loc. cit.*) to our values of K_d we obtained the following values for the distance of closest approach of the ions: $CaOH^+$ 2·55 A., $BaOH^+$ 5·55 A., TlOH 1·23 A. The corresponding sums of the crystallographic radii are

$CaOH^+$ 2·52 A., $BaOH^+$ 2·88 A., TlOH 2·97 A. This shows clearly that an electrostatic explanation is adequate for the formation of $CaOH^+$ and $BaOH^+$, but that covalent forces must be involved in the formation of TlOH.

Our thanks are due to the Department of Scientific and Industrial Research for a grant to one of us (J. E. P.).

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85. *An X-Ray and Thermal Examination of the Glycerides. Part X. Symmetrical Mono-oleoyl and Monoelaidoyl Disaturated Triglycerides.*

By T. MALKIN and B. R. WILSON.

2-Oleo-distearin, -dipalmitin, and -dimyristin exist in five solid modifications, namely, vitreous, α, β″, β′, and β, in order of ascending m. p. Thus, they differ from triglycerides previously studied, which exist in four forms; cf. Part IX, *J.*, 1948, 985. The suggestion of Lutton (*J. Amer. Chem. Soc.*, 1946, **68**, 676) that only three forms exist, cannot, therefore, be sustained. Divergent results of Filer, Sidhu, Daubert, and Longenecker (*ibid.*, p. 167) are shown to be probably due to the presence of diglycerides in their specimens. As was expected (Part IX, *loc. cit.*), *2-elaido-distearin* and *-dipalmitin* are similar to their saturated analogues in their structure and polymorphism.

DAUBERT and CLARKE (*J. Amer. Chem. Soc.*, 1944, **66**, 690) showed by means of cooling and heating curves that 2-oleoyl disaturated glycerides (saturated acids C 10, 12, 14, 16, and 18) exist in four solid modifications, and this was supported by the work of Meara (*J.*, 1945, 22), who reported four m. p.s for 2-oleodistearin isolated from six different natural fats. Later, Filer *et al.* (*loc. cit.*) recorded *X*-ray data for certain of the above glycerides, and shortly afterwards, Lutton (*loc. cit.*), who examined 2-oleodistearin thermally and with *X*-rays, concluded that only three forms exist.* Apart from this difference concerning the number of polymorphs, there are discrepancies in the *X*-ray results of Lutton and Filer *et al.* Thus, the long spacings given by the latter are twice as great as those of Lutton, and the side spacings given for the form of oleodistearin of m. p. 37° are entirely different. It was clearly desirable, therefore, to re-examine these compounds.

Although 2-elaido-disaturated glycerides are not known to exist naturally, we thought it of interest to include them in our study, in view of the probable similarity to their saturated analogues.

Thermal Examination.—Cooling and heating curves taken in the manner described in Part I (*J.*, 1934, 668) showed no unusual features, and were rather similar to those given in Fig. 1, Part IV (*J.*, 1939, 103) for 2-myristodipalmitin and 2-laurodimyristin, the main characteristic of which is the rapid transitions of vitreous ⟶ α ⟶ β′-form, shown by an unusually large rise on the cooling curve during solidification. Apart from a few minor differences in temperature, our results are in good agreement with those of Daubert and Clarke (*loc. cit.*) (cf. Table I), whose curves for 2-oleodimyristin, which show clearly the existence of four solid modifications, give an excellent picture of the behaviour of this group.

One important point, however, appears to have escaped these authors, namely, that the highest m. p. obtained from the curves is almost invariably two or three degrees lower than that of specimens crystallised slowly from solvents, and we find that the four forms shown by the curves do not include the highest-melting stable β-form. Thus, five forms exist, which we term, in harmony with previous nomenclature, vitreous, α, β″, β′, and β, in order of increasing m. p.

2-Oleodimyristin.—The cooling curve (ice-jacketed) shows separation in the α-form, followed by a rise in temperature to the neighbourhood of the β″-m. p., due to transitions α ⟶ β″, β″ ⟶ β′. The heating curve taken immediately after cooling shows a slight indication of the presence of β″-form, but the main arrest is at the β′ m. p. With a steeper cooling gradient (ice and salt) an arrest occurs at the vitreous m. p., and the heating curve then shows arrests at the α, β″, and β m. p.s.

* *Added, October 26th*, 1948.—From a recent paper (*J. Amer. Chem. Soc.*, 1948, **70**, 2441), it seems probable that Dr. Lutton's failure to observe forms reported by other workers is due to the rapidity with which his heating curves are taken, since this tends to smooth out details. Thus, his curves 2 and 3, Fig. 2 (*loc. cit.*) give some evidence of arrests at 59° (α-form) and 65° (β′-form) respectively, and in our experience these arrests would be much more marked if the curves were taken about three times more slowly (the normal rate in this laboratory).

2-*Oleodipalmitin*.—Cooling to room temperature (15°), the curve shows separation of α-form, changing rapidly to β″-form with sharp rise in temperature. The heating curve shows the presence of β″- and β′-forms.

2-*Oleodistearin*.—On cooling to room temperature (18°) there is an arrest at the α-m. p., followed at first by a slight fall in temperature, and then by a sharp rise to 37—38°, due to α ⟶ β″ transition. The heating curve shows only one arrest, at the β″-m. p. Thus, the transition β″ ⟶ β′ is very slow, but, if the β″-form is kept for a few hours just below its m. p., the curve then shows an arrest at the β′-m. p.

2-*Elaido-dipalmitin and -distearin*.—As anticipated in Part VIII (*loc. cit.*), these are similar to the related 2-stearodipalmitin and tristearin, and exist in four forms, *viz.*, vitreous, α, β′, and β. Their m. p.s are lower than those of the saturated compounds, and, in harmony with this, the various transitions, particularly vitreous ⟶ α-form, are more rapid.

Curves for both compounds are much alike. Cooling to room temperature, the vitreous form separates first, and changes rapidly to the α-form, since a heating curve taken immediately after cooling shows only α, β′, and β arrests. With a smaller cooling gradient, the α-form is the first to separate.

M. p.s of the various forms, checked by the usual capillary method, are given in Table I, the values in parentheses being those of Daubert and Clarke (*loc. cit.*).

TABLE I.

	Vitreous.	α.	β″.	β′.	β.
2-Oleodimyristin	2·0 (2·1)	11·0 (12·3)	19·0 (21·5)	26·5 (26·3)	28·5
2-Oleodipalmitin.....	12·0 (12·0)	21·5 (20·8)	29·0 (30·4)	35·0 (35·2)	37·5
2-Oleodistearin	23·0 (22·3)	29·5 (29·8)	37·0 (37·0) (37·6)	41·5 (41·6)	43·5
2-*Elaidodipalmitin* *	33·0	42·0	—	52·5	55·0
2-*Elaidodistearin* †	40·0	46·0	—	58·0	61·0

* (Found: C, 76·5; H, 11·8. $C_{53}H_{100}O_6$ requires C, 76·5; H, 12·1%.)
† (Found: C, 77·07; H, 12·01. $C_{57}H_{108}O_6$ requires C, 77·01; H, 12·3%.)

X-*Ray Investigation*.—This was carried out as described in earlier papers, Parts I (*loc. cit.*) and II (*J.*, 1936, 1628), using pressed and melted layers and rods. In addition to the method described in Part II, rods are conveniently made by melting and cooling the specimen in a m. p. capillary tube, and ejecting it, after conversion into any particular form, by means of a thin steel rod. Our data are given in Table II.

TABLE II.

	Form.	Long spacing, A.	Side spacings, A.
2-Oleodimyristin [1]	β′	39·1	3·92s, 4·23s.
,, ...	β	56·7	3·68m, 3·84m, 4·04m, 4·58vs, 5·17w, 5·43m.
,, impure	Fig. 7		3·57m, 3·74m, 4·01m, 4·26s, 4·40m.
2-Oleodipalmitin [3]	β″	68·5	3·58m, 3·87vs, 4·42m, 4·74s, 5·21w.
,, ...	β′	42·1	3·88m, 4·14m, 4·35s.
,, ...	β	60·7	3·7m, 3·8w, 4·0m, 4·56vs, 5·45m.
2-Oleodistearin [3]	α	50·3	4·17s.
	β″	72·5	3·58m, 3·88vs, 4·47m, 4·74s, 5·22w.
	β′	45·2	3·85m, 4·11m, 4·32s.
	β	64·8	3·66m, 3·84m, 4·02m, 4·58vs, 5·44m.
2-Elaidodipalmitin [2]	β′	44·7	3·8m, 4·18s.
	β	42·7	3·77s, 4·04w, 4·17s, 4·34m.
2-Elaidodistearin	α	51·2	4·14s.
	β′	47·2	3·8m, 4·17s.
	β	44·9	3·66m, 3·85m, 4·00w, 4·57s, 5·31m.

s = strong, vs = very strong, m = moderate, w = weak.

[1] α- and β″-Forms unstable at room temperature.
[2] α-Form unstable at room temperature.
[3] A beautifully crystalline specimen from *Garcinia indica*, sent to us in 1939 by Professor Hilditch, gave the same spacings.

Discussion.—The plate, which shows various side spacings, illustrates some of the more important points. Thus, contrary to Lutton's suggestion of the existence of only three crystalline forms, Figs. 1, 2, 3, and 4 show the definite existence of four (to which must be added the vitreous form). Side spacings of oleodipalmitin are indistinguishable from Figs. 2, 3, and 4,

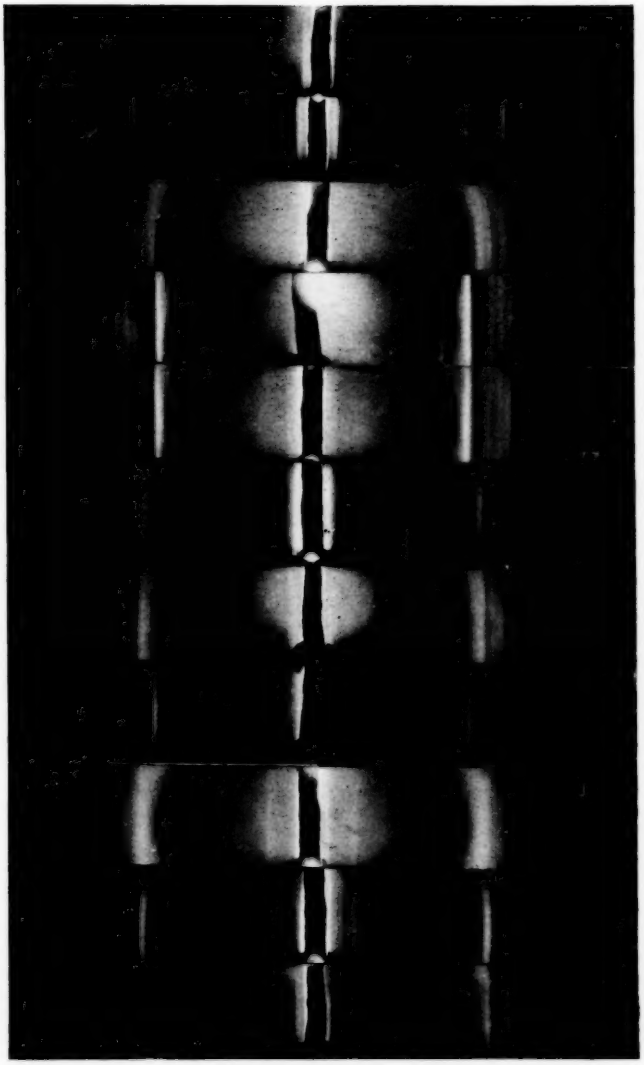


FIG.

1 2-*Olcodistearin*, α

2 ,, , β″

3 ,, , β′

4 ,, , β

5 2-*Olcodimyristin*, β

6 ,, , β′

7 ,, 1·3-*Dimyristin*

8 2-*Elaidodistearin*, β

9 ,, , β′

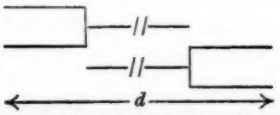
10 ,, , α

11 2-*Elaidodipalmitin*, β

[*To face p.* 370

and all three oleo-compounds are alike in their stable β-form (cf. Figs. 4 and 5). Fig. 7 (impure 2-oleodimyristin, melted rod) is of interest since, within experimental error, the spacings are those given by Filer *et al.*, *loc. cit.* In search of an explanation of the failure of these workers to obtain the spacings shown in Figs. 5 and 6, for 2-oleodimyristin, we added to our specimen some 3—4% of 1 : 3-dimyristin, the most likely impurity, with the result shown. Their failure to obtain the side spacings shown in Fig. 2 (β″-form) for oleodipalmitin and oleodistearin would also appear to be due to contamination with diglyceride, as the spacings they give are of the same spurious type as Fig. 7. Molten specimens of the above two glycerides, allowed to cool to room temperature, always give the spacings shown in Fig. 2.

Our long spacings support Lutton's view of a triple chain length structure for the β″ and β-forms, *viz.* :



cf. Part VIII (—//— = oleoyl).

Filer *et al.* proposed sextuple chain length is based on the presence of a single weak order, not observed by Lutton, lying midway between Lutton's first and second orders, which consequently doubles *d*, the distance between the reflecting planes. This weak order could be the first order of the diglyceride, which appears to be present as an impurity, but we are more inclined to the view that it is the first order of the β′-form. Frequently we find orders of both β and β′-forms present on photographs of oleodimyristin, particularly from melted layers, and even from pressed layers of rapidly crystallised material. Normally, the β-form separates from solvents, but rapid cooling often gives β′- and β-forms, and not infrequently the β′-form only. In fact, one of our methods of obtaining β′-forms for glycerides generally, when other methods fail, is to crystallise rapidly from alcohol. It will be seen from Table II that the long spacings of the β′-forms are roughly two-thirds the magnitude of those of the β-forms, and therefore the first order of the former lies almost midway between the first and second order of the latter.

Our only disagreement with the *X*-ray data of Lutton concerns the long spacing of 80 A. for the α-form of oleodistearin, for which we find no evidence. Our own value of 50·3 A. agrees well with the length of a single molecule, lying vertically across the reflecting planes.

The data for β′-forms, not observed by Lutton, or by Filer *et al.*, are of interest in that they, too, correspond with the single molecular structure proposed by Clarkson and Malkin, as distinct from the triple chain length structure above, and, in view of the observations on this point in Part VIII, it is noteworthy that in spite of the presence of a non-linear *cis*-unsaturated chain, this simple structure is not excluded, albeit only in a metastable form.

The *X*-ray data for 2-elaidodistearin and 2-elaidodipalmitin emphasise again (cf. Part VIII) the great similarity of structures containing elaidoyl and stearoyl radicals. Figs. 8, 9, 10, and 11 are indistinguishable from the corresponding photographs of tristearin and 2-stearodipalmitin (Part IV, *J.*, 1939, 103) respectively. Indeed, it would be extremely difficult to distinguish elaidodistearin from tristearin or elaidodipalmitin from stearodipalmitin by *X*-rays alone, although, of course, m. p.s do so readily.

Experimental.

Preparation of Glycerides.—These were made by the acylation of 1 : 3-diglycerides, the latter being prepared as described in Part III (*J.*, 1937, 1409). The acid chlorides were made by the action of oxalyl chloride on the acids (Adams and Uhlich, *J. Amer. Chem. Soc.*, 1920, **42**, 599). Owing to the sluggish reactivity of the 2-hydroxyl group of the diglyceride, and the impossibility of separating tri- and di-glycerides by crystallisation, these apparently simple preparations are not without their difficulties. Thus, Amberger and Bromig (*Biochem. Z.*, 1922, **130**, 252) isolated only unchanged diglyceride after treating 1 : 3-distearin with oleoyl chloride in quinoline and pyridine at room temperature for several days, and although Jackson, Daubert, King, and Longenecker (*J. Amer. Chem. Soc.*, 1944, **66**, 289) obtained yields of 75% by heating the reagents at 70—85° for 3—6 hours, their products, which are presumably those used by Filer *et al.* (*loc. cit.*), appear to contain diglycerides. In our experience, the only method of obtaining a pure final product is to use an extravagant excess of acid chloride, since we find that large amounts of oleic or elaidic acid are much more readily removed than traces of diglyceride. Two parts by weight of acid chloride to one of diglyceride yielded satisfactory products. The following preparation is typical.

2-*Oleodistearin.*—Oleoyl chloride (2 g.) in dry benzene (50 c.c.) was added to 1 : 3-distearin (1 g.) in warm dry benzene (50 c.c.). Dry pyridine (3 c.c.) was then added, and the mixture refluxed for 2 hours on the water-bath. After 48 hours, it was again refluxed for an hour. Water and ether were then added to the cold mixture, in which was suspended pyridine hydrochloride, and after treatment with dilute sulphuric acid to remove pyridine, and washing until neutral with water, the ethereal benzene solution was dried

(Na_2SO_4). After removal of solvents, the residue was crystallised twice from 100 c.c. of absolute alcohol and thrice slowly from 25 c.c. of "AnalaR" acetone. Yield, 1·15 g. of colourless, long thin prisms, m. p. 43·5° (81%). Alcohol containing a little benzene is also a good final solvent.

The other glycerides were made similarly, the only variation being in the amounts of solvent used for crystallisation, which is reduced for palmitin and myristin compounds. All crystallise in long thin prisms.

Elaidoyl Chloride.—Elaidic acid (5 g.) and oxalyl chloride (7·5 g.; 5 c.c.) were refluxed on the water-bath for 2 hours, a calcium chloride tube being attached to the condenser. Excess of oxalyl chloride was then removed, using the water-pump, and the residue was transferred to a small Claisen flask and distilled under greatly reduced pressure. Yield 5·1 g.; b. p. 130·5—131·5°/0·01 mm.

We gratefully acknowledge a generous gift of allanblackia fat, our source of oleic acid, from Professor T. P. Hilditch, F.R.S., and thank both him and Dr. M. L. Meara for their valuable advice on the preparation of pure oleic acid from it. We also thank the Royal Society and the Colston Society for grants.

THE UNIVERSITY, BRISTOL. [*Received, April 7th*, 1948.]

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86. *Nitrogen Utilisation and Growth of Coliform Bacteria. Part I. Adaptation to Growth in Ammonium Salt Media.*

By G. A. MORRISON and SIR CYRIL HINSHELWOOD.

Certain strains of *Bact. coli* which grow readily in a glucose–phosphate–asparagine medium require training before they will grow with ammonium salts as sole nitrogen source. The training process is shown to be associated chiefly with the overcoming of a long initial lag. The phenomena belong to the type encountered in the training of *Bact. coli mutabile* to lactose or of *Bact. lactis ærogenes* to D-arabinose.

THIS series of studies is concerned with the utilisation of ammonia and of amino-acids by coliform bacteria.

Some of these bacteria, for example, certain strains of *Bact. coli*, utilise ammonium salts in growth with great difficulty until they have been "trained". The method of training usually employed in this laboratory has been to cultivate the bacteria in media containing mixtures of asparagine and ammonium sulphate as the nitrogen source, and, in the course of successive sub-cultures, to reduce the proportion of asparagine gradually to zero.

The first problem to which it seemed proper to give attention was the nature of the adaptive process involved in this training to grow with ammonium salts as the sole nitrogen source.

Apart from its bearing upon the question of nitrogen metabolism, this problem is of interest in connexion with the systematic study of adaptive processes in general.

These processes, which hitherto have been investigated chiefly in relation to changed carbon sources, may conform to several different patterns. In one type, exemplified by *Bact. coli mutabile* and lactose (Massini, *Arch. Hyg.*, 1907, **61**, 250; Postgate and Hinshelwood, *Trans. Faraday Soc.*, 1946, **42**, 45) and by *Bact. lactis ærogenes* and D-arabinose (Cooke and Hinshelwood, *ibid.*, in the press; Jackson and Hinshelwood, *ibid.*, in the press), there is on the first sub-culture into the medium with the new source a very long lag (several days) which, once growth has taken place, does not occur in subsequent sub-cultures. This may be referred to as Type I. In Type II, exemplified by *Bact. lactis ærogenes* with glycerol (Lodge and Hinshelwood, *Trans. Faraday Soc.*, 1944, **40**, 571; Cooke and Hinshelwood, *ibid.* in the press) or with nitrate as a new nitrogen source (Lewis and Hinshelwood, *J.*, 1948, 824), there is no abnormal lag, and growth, in proper conditions, starts at once, but at a rate which is well below optimal and improves in successive sub-cultures. This type is often characterised, in the early stages of the training, by growth curves showing discontinuities.

The usual procedure did not show clearly whether training to utilise ammonia belonged to Type I or to Type II or whether it conformed to yet another type. Experiments show that, in fact, it conforms rather closely to Type I.

Training Experiments.—The methods used in the work to be described were similar to those given in previous papers from this laboratory. The bacteria were grown in aerated synthetic media at 40·0°. The most informative experiments were those made with a pure strain of *Bact. coli*, referred to as H, isolated by Dr. R. L. Vollum who kindly placed it at our disposal. This strain proved very suitable for the investigation.

Parallel inocula were made into two glucose–phosphate–magnesium sulphate media, containing respectively asparagine and ammonium sulphate as nitrogen sources. *Bact. coli* being normally fully adapted to use the former, the *difference* in lags, ΔL, provides a criterion of

the degree of adaptation to ammonia. The asparagine media undoubtedly produce ammonia during growth and so are equivalent to mixed media. At the first pair of parallel sub-cultures ΔL was 1780 minutes. Inocula were then taken from the ammonia medium during logarithmic growth, and transferred in parallel to the asparagine and to the ammonia medium: ΔL was now 10 minutes only. It thus seems that once the very long initial lag in the ammonium salt medium has been overcome it need not be traversed again (Type I).

The question now arises as to what occurs during the conventional training in a mixed ammonia–asparagine medium. The figures in Table I show that the training achieved in this process depends essentially upon the successive *periods of rest* in the asparagine medium, and that the actual *growth* in asparagine is irrelevant. This result is completely parallel to what has been found with *Bact. lactis ærogenes* and D-arabinose (Cooke and Hinshelwood, *ibid.*, in the press; Jackson and Hinshelwood, in the press).

Parallel sub-cultures were then made from a bouillon culture of H into an alanine medium and an ammonium salt medium.

TABLE I.

Bact. coli (Strain H), sub-cultured in asparagine, and tested for lag in the ammonium salt medium at each stage. Re-inoculation in the asparagine medium made during growth to eliminate stationary phase.

Number of passages in asparagine medium.	Sum of lags in asparagine (mins.) (I).	Sum of growth times in asparagine (mins.).	Lag (mins.) before growth in test in ammonium salt medium (II).	I + II.
0	0	0	5460	5460
1	3680	560	1060	4740
2	4010	980	980	4990
3	4310	1390	730	5040
4	4610	1530	400	5010

The first sub-culture directly into ammonia was attended by a lag of 52 hours. Passage through alanine in serial sub-cultures merely allowed this time to be passed with intermissions for growth rather than in one stretch, as is shown by Table II.

TABLE II.

Total time in (hours).	Time of active growth in alanine (approx.) (hours).	Total resting time (hours) in alanine (I).	Lag in ammonium sulphate medium (hours) (II).	I + II.
0	0	0	52	52
40	4	36	23	59
65	8	57	1	58

The conclusion is that before ammonia can be utilised the bacterial substance must spend the required length of time at rest in the medium without an alternative nitrogen source to allow growth by another mechanism.

Essentially similar results were obtained with two other strains of *Bact. coli*. With a strain, M, for example, three sub-cultures in the asparagine medium had reduced the lag in ammonia to within 16 minutes of that in asparagine, the initial value of ΔL having been nearly 8000 minutes. When M was inoculated for the first time into the ammonia medium growth was slow and erratic, even after the lag of 9000 minutes. A second pair of parallel sub-culutres into ammonia and asparagine (of cells which had not been passed through asparagine at all) gave a value of ΔL of 140 minutes only. This confirms once more that the behaviour conforms to Type I.

Even when the initial long lag has been completely removed by standing in the ammonia medium, or by suitable sub-culturing in the mixed medium, the bacteria are not necessarily fully adapted in respect of growth rate (mean generation time) or in respect of the power to multiply to the maximum possible population in the given medium. This normally requires more prolonged training (an argument, incidentally, against the view that the disappearance of the lag is due simply to the selection of a " mutant ").

With H, for example, the first growth rate in ammonia corresponded to a mean generation time of 47 minutes, and the next to 47 minutes also. After repeated sub-culture the value settled down to 42 minutes.

Rather more detailed observations were made with M. Some of these are recorded in Table III.

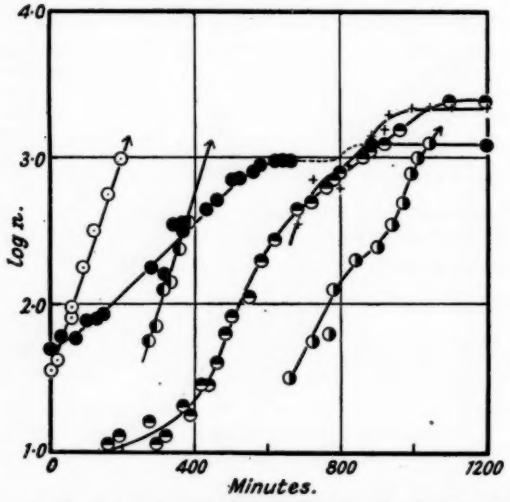
The results in Table III refer to serial sub-cultures in asparagine (with the small amounts of ammonia inevitably present during growth in this medium). When the strain M was

TABLE III.

Strain M. Trained in asparagine (+ ammonia).
Tested in asparagine and in ammonium sulphate.

Number of sub-cultures in asparagine.	Test in asparagine. M.g.t.* (mins.).	Total population.‡	ΔL (mins.).	Test in ammonium sulphate. M.g.t. (mins.).	Total population.‡
0	44	1100	8000	Erratic and † long	
1	29	2000	85	33	140
2	—	2000	—	—	400
3	—	2000	16	34	1100
4	—	2000	—	—	2000
5	29	2500	−35	29	2500
13	—	2500	20	29	2500
20	29	2500	10	29	2500

* M.g.t. = mean generation time.
† Formation of filamentous cells.
‡ The unit is $1{\cdot}25 \times 10^6$ cells/ml.



Successive sub-cultures in the ammonium sulphate medium, showing the development of the true logarithmic growth.

○ *30th Sub-culture.* ◐ *20th Sub-culture.*

The other (non-linear) curves represent early sub-cultures with irregular growth.

N.B.—*Time scales have arbitrary zeros.*

sub-cultured in the ammonium salt medium alone, the history of the training was somewhat different. The mean generation time was at first in the neighbourhood of 60 minutes, and by the twentieth sub-culture had settled down to a steady value of 38 minutes. The true logarithmic form of growth curve is only established as the training becomes complete (see Fig.). The history of the training has here, rather remarkably, a definite influence on the final equilibrium state. The two trained sub-strains were tested by Dr. Vollum, to whom we are indebted for the information that in all the usual diagnostic tests they showed identical behaviour, apart from a tendency of the strain trained directly to ammonia to yield mucoid colonies on deoxycholate–citrate agar. There is thus no question of infection by a foreign organism.

Preservation of the parent strain M in bouillon caused gradual training to ammonia—in all probability in a way corresponding to that shown in amino-acid media. It was of some interest to ascertain to what extent this change affected the whole population. The culture was therefore plated and nine colonies were selected and tested for lag in the ammonium sulphate and the asparagine medium respectively, the difference, ΔL, serving as a criterion of training to the former. The results (expressed in minutes) were: 20, 50, 50, 100, 100, 150, 150, 200,

ca. 1000, which may be compared with the original value of several thousand minutes. The training is therefore spread over the bulk of the population.

Conclusion.—The general conclusion to be drawn from all the experiments described is that adaptation to ammonia is essentially an adjustment whereby a long initial lag is overcome, the utilisation of ammonia depending upon the presence of certain intermediates not necessarily present during growth in other circumstances. Growth in asparagine almost certainly exposes the cells to the action of ammonia, but it is only during the resting periods rather than during active growth in asparagine that the processes leading to the termination of the lag in ammonia utilisation can go on undisturbed.

Once this lag is over, growth with ammonia utilisation takes place and, strictly speaking, this is the period when the modifications in cell material constituting the real adaptation occur. These growth-linked changes ensure that the long lag need not be traversed again.

The elimination of the long initial lag does not complete the adaptation, and the optimum growth rate throughout the logarithmic phase is only reached after further sub-cultures in the ammonia medium. In the intermediate stages the growth curves show arrests indicating that more than one process is in need of further adjustment. This observation and the fact that training, at a quite early stage, is distributed over the bulk of the population, are on the whole more easily compatible with the hypothesis of direct adaptation than with that of spontaneous mutations.

PHYSICAL CHEMISTRY LABORATORY, OXFORD UNIVERSITY. [*Received, May 18th,* 1948.]

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87. *Nitrogen Utilisation and Growth of Coliform Bacteria. Part II. Relation between Growth and Deaminase Activity.*

By G. A. MORRISON and SIR CYRIL HINSHELWOOD.

The development of lag in ageing cultures of *Bact. coli* is not necessarily associated with decay of deaminase activity; nor does recovery of decayed deaminase activity on sub-culture occur until active growth sets in.

Optimum deaminase activity towards a given amino-acid is in general only shown by strains which have been specifically trained by serial sub-culture in its presence, but growth in a given amino-acid usually occurs at a greater rate than ammonia can be furnished by deamination. The amino-acid has two functions the relative importance of which varies from case to case, namely, to provide ammonia and to be utilised directly.

THERE is a well-defined correlation between growth of *Bact. lactis ærogenes* with various carbon sources and its dehydrogenase activity towards them (Davies and Hinshelwood, *Trans. Faraday Soc.*, 1947, **43**, 257; Cooke and Hinshelwood, *ibid.*, p. 733).

This section of the present work explores the connexion between utilisation of various amino-acids and the deaminase activity of *Bact. coli* towards them.

The strain used was derived from M referred to in Part I and was trained to asparagine and ammonia by repeated sub-culture in a glucose–phosphate–magnesium sulphate medium containing the former.

Deaminase activity and growth characteristics were then determined for this strain and for derived strains trained to various other amino-acids.

Method.—Growth rates, lags and total populations were determined in the usual way at 40·0°.

Deaminase activities were measured with preparations of cells centrifuged from the appropriate cultures, washed with isotonic saline, suspended in a little water and stirred by aeration. The heavy suspension thus obtained was added to a medium containing all the normal constituents for growth except glucose (phosphate, magnesium sulphate, amino-acid under test). The count was adjusted to a value suitable for the determination (100—500 million per ml. being convenient according to circumstances).

Samples were taken as soon as possible after the addition of the cells and at intervals of about 15 minutes, the ammonia formed being estimated by Conway and O'Malley's method (*Biochem. J.*, 1942, **36**, 655). 1 Ml. of the sample was immediately pipetted into the outer compartment of the Conway dish and 1 ml. of the saturated potassium metaborate added, the determination being then completed in the standard manner. Blank tests gave values ranging from 0·0 to 1·5 mg./l. of ammonia. The results on deamination rate are conveniently expressed in mg./l. of ammonia produced per minute for each 1·25 million cells per ml. (corresponding to unit

hæmocytometer count). Some typical measurements are given in Fig. 1, and Table I shows that the activity so measured is independent of the actual cell count used in the experiment.

TABLE I.

Deaminase activity and cell count.

Count during test in 10^6 per ml.	162	250	625
$A \times 10^4$	8·8	8·9	8·8

Training and Deaminase Activity.—The strain was trained by serial sub-culture in the appropriate media.

Table II shows the deaminase activities of the various trained strains towards the different amino-acids.

TABLE II.

Deaminase activity of trained sub-strains.

	Deaminase activity $\times 10^4$.			
	Asparagine.	Aspartic acid.	Alanine.	Glycine.
Strain trained to asparagine only	8·9	1·6	1·6	0·5
Strains trained to asparagine and aspartic acid ...	26·0	15·0	8·4	4·4
,, ,, ,, alanine	18·3	6·1	13·3	2·7
,, ,, ,, glycine	13·5	4·0	4·7	8·8

From Table II emerge the conclusions (*a*) that the activity towards asparagine can be still further increased by additional training especially in aspartic acid, (*b*) that in general *some* increase in activity towards all the amino-acids is brought about by training to any one of them, but that (*c*) *optimal* activity towards aspartic acid, alanine or glycine is only reached by strains which have been previously trained by serial sub-culture in the presence of that particular nitrogen source. The specificity, though considerable, is on the whole less marked than that appearing in the dehydrogenase activity of strains trained to various carbon sources.

Growth Characteristics.—The growth characteristics of the various trained sub-strains are recorded in Table III.

TABLE III.

Growth characteristics of trained sub-strains.

ΔL = lag in test medium minus lag in asparagine (minutes); m.g.t. = mean generation time (minutes); n_s = total bacterial population at end of growth ($n = 1$ corresponds to 1·25 million per ml.).

	Tested in											
	Asparagine.			Aspartic acid.			Alanine.			Glycine.		
	ΔL.	M.g.t.	n_s.	ΔL.	M.g.t.	n_s.	ΔL.	M.g.t.	n_s.	ΔL.	M.g.t.	n_s.
Trained to asparagine only	0	29	2700	10	73	2000	60	31	2200	10	(113)	570 (1000)
Trained to asparagine plus aspartic acid	0	25	2400	0	38	2000	110	35	2100	100	(61)	580 (1000)
Trained to asparagine plus alanine	0	30	2700	25	73	2000	55	30	2200	35	(153)	650 (1000)
Trained to asparagine plus glycine	0	33	2700	10	70	2000	90	33	2000	55	52·5	2100

Of the results in Table III the following may be said.

(*a*) The changes in lag are not important, though there is a small tendency for the lags in alanine and glycine to be longer than those in aspartic acid and asparagine.

(*b*) The mean generation time for all strains approaches the optimal in alanine whether or not they have been specifically trained. On the other hand, in glycine and aspartic acid the growth of any but the specifically trained strains is much slower. In glycine, moreover, the phenomenon of broken growth curves appears (Lodge and Hinshelwood, *Trans. Faraday Soc.*, 1944, **40**, 571), the logarithmic form only being developed after considerable training.

(*c*) As far as total population is concerned the differences recorded in n_s are hardly significant. The only specificity is that observed in connexion with the step-wise growth in glycine.

The parallelism between growth rate and deaminase activity is only partial. With glycine and aspartic acid, optimal growth is correlated with optimal deaminase activity, but with

alanine the former seems attainable without the latter, as appears from a comparison of Tables II and III.

Nitrogen Consumption and Cell Count.—It is important for many purposes to know the total increase in bacterial population corresponding to a given utilisation of asparagine or ammonia. Very small inocula of *Bact. coli* (M) were given to media containing varying amounts of asparagine or ammonium sulphate (which have the same molecular weight and the same nitrogen content), and the total populations counted 24 hours after growth had ceased. The results are shown in Fig. 2. From the slope of the curve it is calculated that 1·25 million cells per ml. (hæmocytometer counts of unity) are equivalent to 0·0732 mg./l. of ammonia.

FIG. 1.

Deaminase activity of Bact. coli (M) *towards various substrates.*

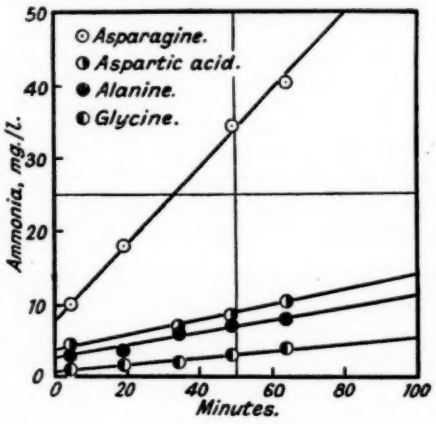
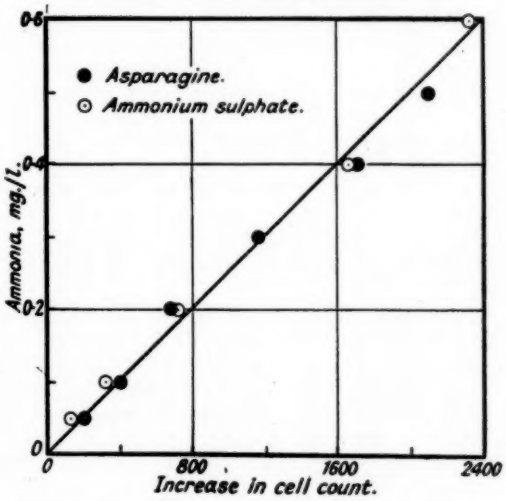


FIG. 2.

Nitrogen utilisation (expressed in terms of NH_3*) for given increases of cell population.*



Decay and Recovery of Deaminase Activity.—The next problem to be considered was the variation of deaminase activity towards asparagine as the cells aged and passed into the "resting" state. In this phase there is a progressive increase in the lag which must occur before growth takes place on inoculation into fresh medium. Table IV shows that the development of lag is *not* normally correlated with loss of deaminase activity, a lag of 49 hours being reached with only a relatively small change in this activity.

TABLE IV.

Variation of deaminase activity with age.

(All measurements made at 40·0°.)

Age of culture, days.	Lag, hours.	Deaminase activity × 10^4. Glucose absent.	Glucose present.
0·9	3·5	8·6—9·2	—
3·9	—	7·8—9·2	6·9—9·0
5·9	16	8·0—8·9	7·2—7·5
7·9	19	8·2—8·7	6·3—7·8
11·9	29	7·1—8·5	6·5—8·1
17·9	49	5·7—7·6	5·7—8·7
26·9	—	4·6—5·1	5·1—6·4

Only after a period of ageing considerably longer than that shown in Table IV does the deaminase activity drop towards zero. At this stage the lag rises rapidly to an infinite value, and, since no sub-cultures are possible, there is good reason to believe that most of the cells are dead. These results are generally similar to those found in the study of dehydrogenase activity (James and Hinshelwood, *Trans. Faraday Soc.*, 1948, **44**, 967).

The recovery of activity of a 78-day old culture with deaminase activity $1·6 \times 10^{-4}$ units was next studied. A suspension of 250 million cells/ml. was made in the full asparagine growth medium, the ammonia concentration and the bacterial count being determined at intervals.

From the results giving the ammonia utilised for a given increase in n (Fig. 2), the ammonia concentration could be corrected for that which might have been formed and subsequently used in growth. Maximum ammonia production could then be plotted against time, and from the tangent to this curve the maximum possible value of the deaminase activity $\frac{1}{n}\frac{d[NH_3]}{dt}$ could be calculated. Some results are given in the first three columns of Table V and show that there is no appreciable recovery before growth sets in.

TABLE V.

Recovery of deaminase activity.

Time (minutes).	Total count, n.	Deaminase activity, $A \times 10^4$.	Viable count, n'.	$\frac{An}{n'} \times 10^4$.
0—150 (6 readings)	178	1·7	38	8·0
200	190	2·5	50	9·5
304	363	6·0	223	9·8
375	660	6·8	520	8·6
436	1520	8·1	1380	8·8

An estimate of the viable count of the initial 78-day old culture by a method described previously (Lodge and Hinshelwood, *J.*, 1943, 213) gave the result that 140 out of 178 cells were dead. The fourth column of the Table gives the viable count, and the last the deaminase activity related to the number of living cells rather than to the total number. The approximate constancy of these results supports the view that the deaminase activity is only seriously lost with the death of the cell and that the recovery is a measure of the production of fresh viable cells.

Deaminase Activity and Growth Rate.—The question now arises as to whether growth can follow the route: amino-acid ⟶ ammonia ⟶ synthesis, or whether direct utilisation of the amino-acid by trans-amination and other reactions occurs.

The relation between the increase of bacterial count and the ammonia consumption is already known, and is expressed by the relation

$$-\frac{d[NH_3]}{dn} = a$$

From this it follows that

$$-\frac{1}{n} \cdot \frac{d[NH_3]}{dt} = \frac{a}{n}\frac{dn}{dt} = ak$$

but $k = 0{\cdot}693/T$, where T = mean generation time. Therefore

$$-\frac{1}{n} \cdot \frac{d[NH_3]}{dt} = \frac{0{\cdot}693a}{T}$$

If this rate of ammonia consumption were provided by the deamination reaction, $-\frac{1}{n}\frac{d[NH_3]}{dt}$ would equal A, the deaminase activity. Thus $A_0 = 0{\cdot}693a/T$, where A_0 is the deaminase activity just able to furnish ammonia at the rate required when the mean generation time is T.

$a = 0{\cdot}0732$, when $[NH_3]$ is expressed in mg./l. and n in units of 1·25 millions/ml. (unit hæmocytometer count).

TABLE VI.

Nitrogen utilisation and deaminase activity.

(A = actual deaminase activity; A_0 = deaminase activity required to supply ammonia fast enough to account for observed growth rate.)

	Growth in: Asparagine.		Aspartic acid.		Alanine.		Glycine.	
	$A \times 10^4$.	$A_0 \times 10^4$.	$A \times 10^4$.	$A_0 \times 10^4$.	$A \times 10^4$.	$A_0 \times 10^4$.	$A \times 10^4$.	$A_0 \times 10^4$.
Strain trained to asparagine only ...	8·9	17·5	1·6	7·0	1·6	16·4	0·5	4·5
Trained to asparagine and aspartic acid...	26·0	20·3	*15·0*	*13·4*	8·4	14·5	4·4	8·6
Trained to asparagine and alanine	18·3	16·9	6·1	7·0	13·3	16·9	3·7	3·3
Trained to asparagine and glycine	13·5	15·5	4·0	7·2	4·7	15·5	*8·8*	*9·7*

From the values of T in Table III and the values of A in Table II the comparisons in Table VI may be worked out.

Consideration of Table VI reveals the following facts.

(*a*) The strain trained to asparagine only cannot deaminate any of the amino-acids rapidly enough to account for the growth rate if growth is supposed to occur by way of ammonia liberation. Some more direct mode of utilisation is therefore operative, probably one involving a trans-amination mechanism.

(*b*) In the sub-strains trained to aspartic acid, alanine or glycine the activity approaches or exceeds that required to account for growth *via* ammonia. With alanine as substrate the direct utilisation appears to be very efficient and no great advantage accrues from the addition or substitution of the deamination mechanism. With glycine, however, the whole character of the growth curves changes when the new mechanism is developed. The present results provide corroborative evidence for the idea of alternative growth mechanisms already advanced on other grounds (Lodge and Hinshelwood, *loc. cit.*, 1944).

(*c*) The behaviour in the asparagine medium requires further consideration. The important point to note is that subsequent training to other amino-acids can improve the deaminase activity towards asparagine itselt without appreciably increasing the corresponding growth rate. This is considered further in the following paragraph.

Deamidation and Deamination of Asparagine.—The two nitrogen atoms in asparagine, $\begin{matrix}CH(NH_2)\cdot CO_2H\\ CH_2\cdot CO\cdot NH_2\end{matrix}$, may obviously be used in different ways.

Application of the Martin and Synge method of partition chromatography, in a way to be described later, showed that, during growth in asparagine, aspartic acid first accumulated and was then consumed again. An estimate could be made of the rate of deamidation of asparagine to aspartic acid and yielded the approximate value of $7{\cdot}0 \times 10^{-4}$ units (on the scale employed for the determination of deaminase activity). If, as a rough approximation, this value for the deamidation rate of asparagine is assumed to remain constant, and the changes accompanying the training to other media are ascribed solely to improvements in the deamination of the aspartic acid part of the system, we should expect the relation: *Total activity towards asparagine in given medium* = 7·0 + *activity towards aspartic acid in that medium.* Table VII shows that this possibility is approximately realised.

TABLE VII.

	$A \times 10^4$ for aspartic acid = B.	B + 7·0.	Observed total activity ($\times 10^4$) to asparagine.
Strain trained to asparagine	1·6	8·6	8·9
Trained to asparagine and aspartic acid...	15·0	22·0	26·0
Trained to asparagine and alanine	6·1	13·1	18·3
Trained to asparagine and glycine	4·0	11·0	13·5

Conclusion.—This part of the work shows clearly that amino-acids in general may be first deaminated by *Bact. coli* to ammonia which is then used in synthesis, or that, alternatively, they may be more directly utilised by trans-amination and other processes. Optimum growth rate of the *Bact. coli* does not necessarily involve optimum deaminase activity. Maximum deaminase activity is only reached after training to the specific substrate. With some amino-acids, *e.g.*, glycine, this is true also of growth rate; with others, however, *e.g.*, with alanine, the optimal growth rate is attained without any training of the deaminase activity. Possibly the three-carbon molecule of alanine is more suitable for direct conversion into essential intermediates than the two-carbon molecule of glycine, whose best rôle in the bacterial economy is the simple provision of nitrogen for reaction with other compounds from the carbon source. That alanine may be able to transfer its amino-nitrogen more easily than glycine is a possibility which must also be borne in mind. Asparagine and aspartic acid (and also glutamic acid) are specially suitable for direct use (see Part III).

PHYSICAL CHEMISTRY LABORATORY, OXFORD UNIVERSITY. [*Received, May 18th*, 1948.]

88. *Nitrogen Utilisation and Growth of Coliform Bacteria. Part III. Nitrogen Utilisation and Lag Phase.*

By G. A. Morrison and Sir Cyril Hinshelwood.

Considerable lag phases in a growth medium consisting of glucose, magnesium, phosphate, and ammonium sulphate may be shown by untrained *Bact. coli*, trained *Bact. coli* which has been allowed to "age", and strains of *Bact. lactis ærogenes* which have been allowed to age or have been irradiated. In all these cases the lag seems to be largely connected with the need for the production from glucose of four- and five-carbon skeletons which can be aminated to give key amino-acids.

The lag may be reduced almost to zero by allowing the cells to remain for the appropriate time in contact with a glucose medium lacking any added nitrogen source, and in the full medium no detectable consumption of ammonia occurs before the very end of the lag, when there are indications that traces of glutamic and aspartic acids appear in the solution. Additions of these acids shorten lags in ammonium sulphate media considerably, glutamic acid being the more effective. (The growth rates with glutamic acid or aspartic acid as sole source of nitrogen are, however, much lower than those observed with ammonium sulphate, the amino-acids being capable of initiating growth by mechanisms which are not the optimal.) Certain carbon compounds which are obvious possible precursors of glutamic or aspartic acid, especially α-ketoglutaric acid, approach the corresponding amino-acids in efficiency in shortening lag, but are never quite as effective as glutamic acid itself.

Ammonia Consumption in Lag Phase.—An old culture of the strain *Bact. coli* M was washed and suspended in glucose–phosphate–magnesium sulphate medium containing ammonium sulphate at $44{\cdot}5 \pm 0{\cdot}5$ mg./l. The ammonia content of samples was determined by Conway and O'Malley's method (*Biochem. J.*, 1942, **36**, 655) at intervals during the lag phase, with results recorded in Table I, which shows that the actual consumption of ammonia before growth sets in is too small to detect.

Table I.

Time (mins.).	log *n*.	NH_3, mg./l.	Time (mins.).	log *n*.	NH_3, mg./l.	Time (mins.).	log *n*.	NH_3, mg./l.
5	2·41	$44{\cdot}5 \pm 0{\cdot}5$	238	2·41	45·2	415	2·55	40·0
50	2·41	45·2	290	2·41	44·5	470	2·67	28·4
140	2·41	41·4	350	2·41	45·2	530	2·96	4·7
200	2·41	44·9						

In view of the small ammonia consumption indicated by this last experiment the following test was made. Inocula from an old culture were transferred in parallel to two media, one complete except for the glucose, the other complete except for the ammonium sulphate. After various intervals of time the media were completed, and the lag before the onset of growth was determined. The results are recorded in Table II, which shows that for the medium containing

Table II.

	Medium initially lacking added nitrogen.		Medium initially lacking glucose.	
Time of completion of medium (minutes).	Lag measured from inoculation.	Lag measured from completion of medium.	Lag measured from inoculation.	Lag measured from completion of medium.
5	363	358	387	382
38	351	313	436	398
67	290	333	—	—
187	386	199	545	358
225	379	154	554	329

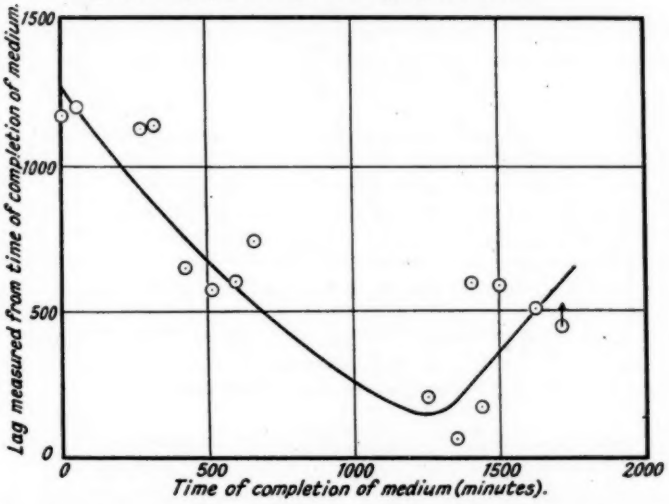
glucose but lacking ammonium sulphate the total lag as measured from the time of *inoculation* is nearly constant, while for the medium lacking glucose there is a constant lag as measured from the time of *completion*. In other words, either no nitrogen is needed for the preparatory processes of the lag phase or the extremely minute amounts contained in the glucose as impurity or carried over in the cells of the inoculum are all that is required.

The results of a similar experiment with a parent culture showing a longer lag are given in Fig. 1. The inoculations were made into medium lacking any added nitrogen. The curve shows that almost the total preparation for growth may be made in the glucose medium before the ammonium sulphate is added, the lag, as measured from the time of *completion* of the medium, reaching a minimum value of almost zero.

Influence of Glutamic Acid and Aspartic Acid on Lag Phase and Growth Rate.—A partition chromatography method to be described later gave indications of the formation of traces of glutamic and aspartic acids at the end of the lag just before growth began in an ammonium sulphate–glucose medium. This led to a series of experiments on the effect on the lag of additions of these substances (these experiments being of course independent of the validity of the chromatographic observations which prompted them).

FIG. 1.

Effect on lag of standing in nitrogen-free medium.



The strain *Bact. coli* M, trained in asparagine, which was referred to in Part I, was inoculated into eight different media in parallel at various times after growth of a parent culture had begun. These media contained glucose, phosphate, magnesium sulphate, together with one of the following nitrogen sources: (1) ammonium sulphate, (2) ammonium sulphate and glutamic acid (G), (3) ammonium sulphate and aspartic acid (A), (4) ammonium sulphate with both glutamic and aspartic acids, (5) asparagine, (6) asparagine and glutamic acid, (7) glutamic acid

TABLE III.

		ΔL.						
Time.	L in Am_2SO_4.	Am_2SO_4 + G. (1 − 2).	Am_2SO_4 + A. (1 − 3).	Am_2SO_4 + A + G. (1 − 4).	Asparagine. (1 − 5).	Asparagine + G. (1 − 6).	G. (1 − 7).	A. (1 − 8).
0	0	0	0	0	0	0	0	0
393	110	90	40	90	40	85	105	60
1188	590	260	130	340	170	340	350	190
1398	650	200	160	310	150	290	235	130

(G), (8) aspartic acid (A). Where the amino-acid was an addition the concentration was approximately 500 mg./l.; where the sole source, it was equivalent in nitrogen to the ammonium sulphate.

The first set of inoculations was made when the count of the parent culture was 195×10^6 cells/ml., the lag at this stage being zero in all the media. As the parent aged, the lag increased most rapidly in the medium (1) containing ammonium sulphate alone, and least rapidly in (4) which contains both glutamic and aspartic acids. Glutamic acid shortens the lag more than aspartic acid but the two effects may be more or less additive. In Table III are recorded the lags, L, in minutes, for the medium (1) and the shortening, ΔL, observed in the various other media.

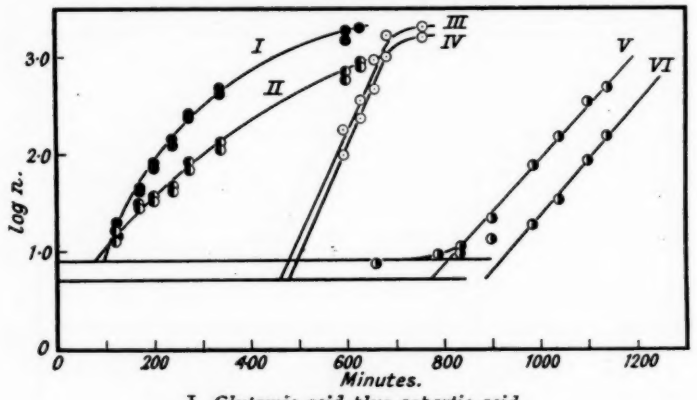
In Table III it is to be noted that (1 − 5) agrees rather closely with (1 − 3) and (1 − 6) with (1 − 4). Thus the results for asparagine are substantially the same as those for ammonium sulphate with addition of aspartic acid.

The rate of growth in media containing aspartic or glutamic acid as the only nitrogen source

is much lower than in those containing ammonium sulphate or asparagine. The mean generation time with glutamic acid alone is initially about 67 minutes, increasing slightly as growth proceeds. With aspartic acid alone the mean generation time is about 72 minutes for cultures showing a short lag. If the age of the parent culture is such that the lag is long, the subsequent growth is more rapid. It appears, therefore, that aspartic acid may *initiate* growth by a

FIG. 2.

Growth in various nitrogen sources (Bact. coli).



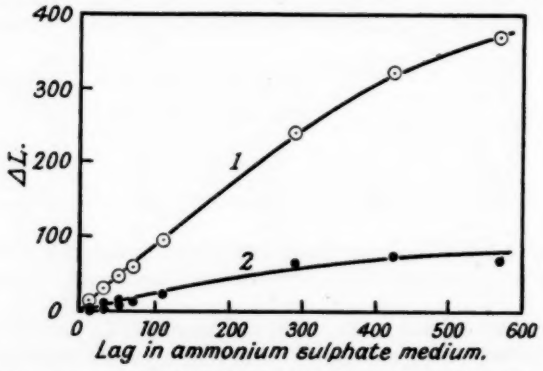
I. *Glutamic acid plus aspartic acid.*
II. *Glutamic acid.*
III and IV. *Asparagine.*
V and VI. *Aspartic acid.*

mechanism which is not the optimum one. During the longer lags other intermediates are formed which permit growth by a more rapid mechanism. Indeed, occasionally a long lag, in media containing traces of aspartic acid, is followed by growth according to a composite curve, a period of slow multiplication being superseded at a certain point by a more rapid one.

Some of the lag and growth rate relations for the strain *Bact. coli* (M) are shown in Fig. 2.

FIG. 3.

Effect of amino-acid additions on growth of Bact. lactis ærogenes.



Upper curve: glutamic acid or glutamic–aspartic acid mixtures.
Lower curve: aspartic acid.

Similar experiments were next made with a strain of *Bact. lactis ærogenes* which has been the subject of previous study in various other respects. Once again, parallel inoculations were made from a parent culture at different times into a series of media.

The nitrogen sources were respectively ammonium sulphate and ammonium sulphate with addition of small amounts of aspartic acid, glutamic acid or a mixture of both. The results are shown in Fig. 3. In general, glutamic acid shortened the lag phase considerably, whereas

aspartic acid had relatively little effect, and the mixture of the two was not appreciably better than glutamic acid alone.

Influence of Related Non-amino-compounds on Lag Phase.—Although aspartic acid and glutamic acid shorten the lag phase, it is not clear whether this effect is due to the actual amino-acids or to their carbon skeletons. Consequently, it was decided to test the influence on lag of suitable acids which are structurally related to these amino-acids but contain no nitrogen.

The most likely substances are the corresponding keto-acids, oxaloacetic and α-ketoglutaric. The latter was prepared by the method given in " Organic Syntheses ". The product was a faintly yellow crystalline solid of m. p. 109° (sharp), which is the value given in the literature. Oxaloacetic acid was prepared in a mixture with malic acid by controlled oxidation of the latter with hydrogen peroxide (Fenton and Jones, *J.*, 1900, **77**, 75). The product was a faintly yellow crystalline solid containing about 30% of oxaloacetic acid.

The strain *Bact. coli* M, trained to asparagine, was inoculated into seven different media in parallel at various times after growth in the parent cultures had begun. The time of inoculation is counted from the moment when the count of the parent cultures was 200×10^6 cells/ml. The media contained glucose, phosphate, magnesium sulphate and ammonium sulphate, together with one of the following additions (concentration approximately 500 mg./l.): (1) no addition, (2) aspartic acid, (3) glutamic acid, (4) malic acid, (5) " oxidised malic acid ", (6) α-ketoglutaric acid, (7) " oxidised malic acid " and α-ketoglutaric acid. Each culture tube contained 26 ml. plus the volume of the additions, and 1 g./l. of ammonia as ammonium sulphate. The results are recorded in Table IV. The lags, L, and differences in lag, ΔL, are given in minutes.

Clearly, glutamic acid is the most efficient (1 — 3) and more so than α-ketoglutaric acid (1 — 6), but quite an important part of the lag reduction is due to the carbon skeleton. Malic acid and aspartic acid are more or less equivalent and the least efficient tested. Oxaloacetic acid is of intermediate efficiency.

Long Lag of Bact. coli *Untrained to Ammonium Salt Media.*—Since the lag which normally develops as the culture ages has been shown to be specially concerned with the utilisation of the carbohydrate, the very long lag shown by certain strains of *Bact. coli* when first transferred

TABLE IV.

Time of inoculation (minutes).	L (1).	ΔL. (1 — 2).	(1 — 3).	(1 — 4).	(1 — 5).	(1 — 6).	(1 — 7).
Series I.							
0	0	0	0	0	0	0	0
500	200	45	185	45	115	130	130
670	200	30	100	30	80	90	90
840	250	30	150	60	115	120	130
1290	290	80	170	30	70	140	120
1680	290	55	150	60	90	110	90
1900	290	50	140	50	85	90	85
Series II.							
780	435	95	285	75	165	195	165
1260	610	270	470	280	340	420	410

to an ammonium salt medium (Part I) seemed likely also to depend upon a difficulty in the appropriate metabolism of glucose. The strain *Bact. coli* H was therefore subjected to further investigation.

Inocula of about 10^6 cells per c.c. from a fresh bouillon culture were transferred to ammonium salt media and to similar media containing α-ketoglutaric acid, at approximately 500 mg./l. The lags in the former were 95—116 hours, but in the latter only 6. In another experiment similar inocula were transferred to media with the following additions, and exhibited the lags given in parentheses: (1) No addition (96 hours), (2) asparagine (40 hours), (3) malic acid (19·5 hours), (4) oxaloacetic acid (22 hours), (5) α-ketoglutaric acid (20 hours).

A further confirmation of the reason for this phenomenon of long lag was provided by various strains of *Bact. lactis ærogenes* isolated by A. R. Peacocke from a culture which had been irradiated with ultra-violet light. These strains showed the phenomenon of a long lag in the ammonium salt medium, and this lag was largely removed by addition of α-ketoglutaric acid. The results will be reported in another paper.

Discussion.—The results described have shown that during the lag phase extremely little

nitrogen is required but that the carbohydrate substrate must be present. This suggests that it is the breakdown of the carbon source to give the appropriate kind of molecules which is of key importance. In this connextion it is worth noting that magnesium ions, which are catalysts for phosphorylations, are also necessary during this period (Pett and Wynne, *Biochem. J.*, 1933, **27**, 1660; Lodge and Hinshelwood, *J.*, 1939, 1692).

From the effects on the lag phase of the various additions it seems quite likely that during this time various compounds are formed from the glucose and that molecules of special importance are those with a five-carbon skeleton. When these reach a sufficient concentration nitrogen can be taken up to give amino-acids and growth starts.

If a substance corresponding to a relatively early link in the metabolic and synthetic chain is added to the medium, it may be as effective as its corresponding amino-acid in shortening the lag, the time required for amination being of no importance compared with other stages. Thus malic acid and aspartic acid have about the same influence. The more effective additions, however, will be those which correspond to later stages of the sequence. Thus, ready-made α-ketoglutaric acid is very active. When the other steps have been by-passed as completely as possible, the amination step itself becomes relatively important, and, accordingly, glutamic acid is even more effective as an addition than the α-ketoglutaric acid from which it could be formed by amination.

A key rôle, it would seem, must be assigned to glutamic acid itself, since of all the substances tested it is the most efficient in reducing the lag. It is superior in this respect to its keto-precursor, but there is little doubt that the prior formation of a keto-group is important, since a given carbon skeleton containing it is more effective than one without.

These conclusions bring the present work into close relation with various well-known facts connected with the biochemistry of yeast, muscle and other systems.

The long lag exhibited by certain strains of *Bact. coli* when first transferred to ammonium salt media is also due largely to an inability to produce required compounds at an adequate rate from the glucose. As these substances are required at definite concentrations before growth can proceed, the apparent inability to utilise the ammonia arises. It is probable that the cells fail to produce the four- and five-carbon compounds at first, and are handicapped consequently in the later stages of the metabolism. The same difficulty may appear with *Bact. lactis ærogenes* after irradiation with ultra-violet light.

The interrelation between the three parts of this work is now clear. In Part I the training of *Bact. coli* to utilise ammonia was shown to be connected with the elimination of a long initial lag. In Part III this lag, as well as the lag developed in older cultures of trained bacteria, was shown to be largely connected with the production from glucose of carbon compounds of well-known biochemical significance such as oxaloacetic acid and α-ketoglutaric acid. The amination of these compounds appears to occur with comparative readiness to give amino-acids such as aspartic acid and glutamic acid which were shown in Part II to be directly used by the cell and not to serve as mere sources of ammonia. On the other hand, acids such as glycine when provided as sole nitrogen sources largely yield ammonia for aminating key carbon compounds. From these considerations follows the somewhat complicated relation between deaminase activity and growth rate in various amino-acids.

We are indebted to Messrs. R. G. Otter and G. Stafford for assistance in the preparations involved in this work.

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89. *Action of Grignard Solutions on* (a) *Naphthasultone,* (b) *Tolylene-3 : 4-sulphonylide, and* (c) *NN'-Diarylsulphonyl Derivatives of Dianthranilide.*

By AHMED MUSTAFA and AHMED MOHAMED GAD.

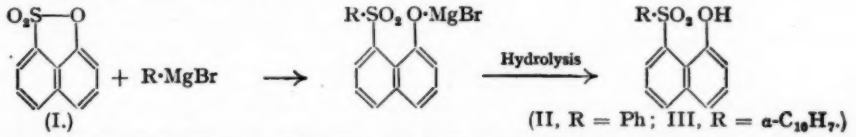
(*a*) 1-Hydroxy-8-phenylsulphonylnaphthalene (II) and 1-hydroxy-8-α-naphthylsulphonylnaphthalene (III) were obtained by the action of phenyl- and α-naphthyl-magnesium bromide respectively on naphthasultone (I).

(*b*) 2-Hydroxy-5-methyldiphenyl sulphone (V) was similarly obtained by the action of phenylmagnesium bromide on tolylene-3 : 4-sulphonylide (IV).

(*c*) The action of Grignard solutions on *NN'*-diarylsulphonyl derivatives of dianthranilide (VI*a*, VI*b*) leads to the formation of *N*-arylsulphonyl derivatives of *o*-aminotriarylcarbinols

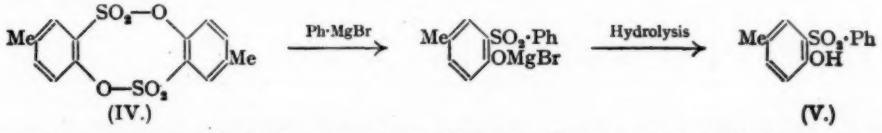
(VII*a*—VII*c*), and 2-toluene-*p*-sulphonamidophenyldimethylcarbinol (VII*d*) is obtained by the action of methylmagnesium iodide on (VI*b*). The latter, when heated with aniline, gives *o*-toluenesulphonamidobenzanilide.

During the investigation of the action of diazomethane on *o*-hydroxydiaryl sulphones and the corresponding *peri*-compounds (Schönberg and Mustafa, *J.*, 1948, 605), 1-hydroxy-8-phenyl- (II) and -8-α-naphthyl-sulphonylnaphthalene (III) were synthesised. The synthesis was carried out by the action of phenyl- and α-naphthyl-magnesium bromide, respectively, on naphthasultone (I), followed by hydrolysis; (II) and (III) react with ethereal diazomethane to form the corresponding methoxy-derivatives (Schönberg and Mustafa, *loc. cit.*), dissolve in aqueous alkalis, and contain active hydrogen.



(I.) (II, R = Ph; III, R = α-$C_{10}H_7$.)

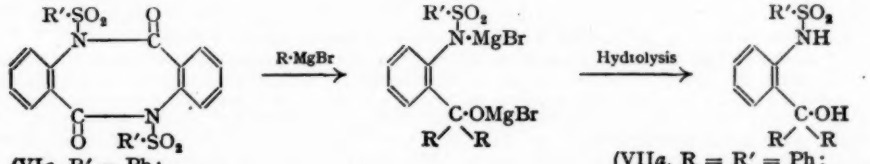
2-Hydroxy-5-methyldiphenyl sulphone (V) was obtained, similarly, by the action of phenylmagnesium bromide on tolylene-3 : 4-sulphonylide (IV), followed by hydrolysis; (V) reacts with ethereal diazomethane to give 2-methoxy-5-methyldiphenylsulphone (Schönberg and Mustafa, *loc. cit.*).



(IV.) (V.)

The action of Grignard solutions on (I) and (IV) constitutes a new method for the preparation of *o*-hydroxydiaryl sulphones and the corresponding *peri*-compounds.

Very little is known about the action of Grignard solutions on *NN'*-diarylsulphonyl derivatives of dianthranilide. We have investigated the action of Grignard solutions on (VI*a*) and (VI*b*) and obtained the corresponding *o-arylsulphonamidotriarylcarbinols* (VII*a*—VII*c*). The action of methylmagnesium iodide on the dianthranilide (VI*b*) yields 2-toluene-*p*-sulphonamidophenyldimethylcarbinol (VII*d*). We believe that the reaction occurs according to the following scheme :



(VI*a*, R′ = Ph; VI*b*, R′ = *p*-C_6H_4Me.)

(VII*a*, R = R′ = Ph; VII*b*, R = Ph, R′ = *p*-C_6H_4Me; VII*c*, R = R′ = *p*-C_6H_4Me; VII*d*, R = Me, R′ = *p*-C_6H_4Me.)

Constitution of the Products obtained (VIIa—VIId).—These products are of analogous structure; 2-toluene-*p*-sulphonamidotriphenylcarbinol (VII*b*) is taken as an example. Its constitution is based on its identity with a synthetic specimen obtained by the action of toluene-*p*-sulphonyl chloride on *o*-aminotriphenylcarbinol. These products are almost colourless, soluble in aqueous alkali (cf. Gilman, "Organic Chemistry," 2nd edtn., 1944, Vol. 1, p. 901), contain an active hydrogen atom and give the expected molecular weights; both (VII*b*) and the synthetic substance, when heated with aniline, gave (probably) bis-(2-toluene-*p*-sulphonamidotriphenylmethyl) ether; (VII*b*) also reacts with ethereal diazomethane (details will be published later).

Action of Aniline on NN′-*Ditoluene*-p-*sulphonyldianthranilide* (VIb).—This reaction affords 2-toluene-*p*-sulphonamidobenzanilide. When aniline is replaced by tetralin, (VI*b*) is recovered unchanged. The anilide was also obtained by the action of aniline on 2-toluene-*p*-sulphonamidobenzoyl chloride in dry benzene.

Experimental.

1-*Hydroxy*-8-*phenylsulphonylnaphthalene* (II).—To an ethereal solution of phenylmagnesium bromide [from magnesium (0·9 g.), bromobenzene (9·4 g.), and dry ether (40 c.c.)], naphthasultone (I) (1·5 g.)

(Erdmann, *Annalen*, 1888, **247**, 306) and dry benzene (30 c.c.) were added. The mixture was refluxed for 3 hours and set aside overnight, then decomposed with cold dilute hydrochloric acid and extracted with ether. The ethereal solution was dried and evaporated, and the residue extracted several times with light petroleum (b. p. 30—50°); it then crystallised from benzene–light petroleum (b. p. 50—70°) in almost colourless crystals, m. p. 140° (Found: C, 67·4; H, 4·0; S, 11·0; active hydrogen, 0·32. $C_{16}H_{12}O_3S$ requires C, 67·6; H, 4·2; S, 11·3; active hydrogen, 0·35%). This *compound* dissolves in aqueous sodium hydroxide solution with a yellow colour and is regenerated on acidification; it is converted into its methyl ether when treated with ethereal diazomethane solution (Schönberg and Mustafa, *loc. cit.*). It is soluble in benzene and ethyl alcohol, difficultly soluble in light petroleum (b. p. 50—70°), and gives no colour when treated with concentrated sulphuric acid.

1-*Hydroxy*-8-*α-naphthylsulphonylnaphthalene* (III).—Similarly, naphthasultone (1 g.) was treated with α-naphthylmagnesium bromide [magnesium (1·2 g.), α-bromonaphthalene (10 g.), dry ether (40 c.c.)]. The *compound* was obtained in colourless crystals from benzene–light petroleum (b. p. 50—70°), m. p. 188° (brown melt) (Found: C, 71·5; H, 4·0; S, 9·7; active hydrogen, 0·26. $C_{20}H_{14}O_3S$ requires C, 71·8; H, 4·2; S, 9·6; active hydrogen, 0·29%). It was difficultly soluble in aqueous sodium hydroxide solution with a brilliant yellow colour, gave no colour with concentrated sulphuric acid, and was methylated like (II). It was soluble in benzene and xylene and difficultly soluble in light petroleum (b. p. 70—80°).

2-*Hydroxy*-5-*methyldiphenyl Sulphone* (V).—By an exactly analogous procedure to that used for (II), the sulphone (V) was obtained by the action of phenylmagnesium bromide on tolylene-3 : 4-sulphonylide (IV) (Anschütz, *Annalen*, 1918, **415**, 76); it formed colourless crystals from benzene–light petroleum (b. p. 50—70°), m. p. 137—138° (Heppenstall and Smiles, *J.*, 1938, 899, gave m. p. 139°); it dissolves readily in benzene, xylene, and hot ethyl alcohol and is difficultly soluble in light petroleum (b. p. 70—80°) (Found: C, 62·7; H, 4·6; S, 12·7. Calc. for $C_{13}H_{12}O_3S$: C, 62·9; H, 4·8; S, 12·9%). It was *O*-methylated by ethereal diazomethane.

Action of Phenylmagnesium Bromide on NN′-*Diphenylsulphonyldianthranilide* (VI*a*).—To an ethereal solution of phenylmagnesium bromide [magnesium (0·9 g.), bromobenzene (9·4 g.) and dry ether (25 c.c.)] dry benzene (50 c.c.) and (VI*a*) (1·5 g.) (Heller, *Ber.*, 1916, **49**, 547) were added. The mixture was refluxed with stirring for 3 hours, the ether being allowed to evaporate slowly. The substance dissolved completely, and the reaction mixture was left overnight and then decomposed with cold water followed by aqueous ammonium chloride solution. The organic matter was extracted with ether, and the residue remaining after evaporation of the ether was washed with light petroleum (b. p. 30—50°) and crystallised from benzene–light petroleum (b. p. 50—70°), forming colourless crystals, m. p. 188° (decomp.; yellow melt) [Found: C, 72·2; H, 4·9; N, 3·3; S, 7·6; active hydrogen, 0·23; *M* (micro-Rast), 402. $C_{25}H_{21}O_3NS$ requires C, 72·3; H, 5·1; N, 3·4; S, 7·7; active hydrogen, 0·24%; *M*, 415].

o-*Phenylsulphonamidotriphenylcarbinol* (VII*a*) is soluble in hot benzene and xylene and difficultly soluble in cold benzene and ethyl alcohol; it gives a reddish-brown colour with concentrated sulphuric acid.

Action of Grignard Solutions on NN′-*Ditoluene*-p-*sulphonyldianthranilide* (VI*b*).—(*a*) *Phenylmagnesium bromide.* The dianthranilide (Anschütz, *loc. cit.*) (1·5 g.) was treated with phenylmagnesium bromide as detailed above. 2-*Toluene*-p-*sulphonamidotriphenylcarbinol* (VII*b*) was obtained in colourless crystals from benzene–light petroleum (b. p. 30—50°), m. p. 196° (yellow melt) [Found: C, 72·5; H, 5·4; N, 3·2; S, 7·3; active hydrogen, 0·21; *M* (micro-Rast), 418. $C_{32}H_{27}O_3NS$ requires C, 72·7; H, 5·4; N, 3·3; S, 7·5; active hydrogen, 0·23%; *M*, 429]; it gives a reddish-brown colour with concentrated sulphuric acid, and its solubility properties are similar to those of (VII*a*).

For comparison (VII*b*) was synthesised as follows. *o*-Aminotriphenylcarbinol (1 g.) (Baeyer and Villiger, *Ber.*, 1904, **37**, 3193), dissolved in the minimum of dry pyridine, was treated with toluene-*p*-sulphonyl chloride. The mixture was heated on a water-bath for 4 hours, kept overnight, and then poured on ice. The oil which separated solidified on cooling and rubbing; it was filtered off, washed several times with light petroleum (b. p. 50—70°), and crystallised from benzene–light petroleum (b. p. 30—50°), forming colourless crystals, m. p. 195°, identical with (VII*b*) (m. p. and mixed m. p. and colour reaction with sulphuric acid) (Found: C, 72·4; H, 5·2; N, 3·3; S, 7·6%).

(*b*) p-*Tolylmagnesium bromide.* 2-*Toluene*-p-*sulphonamidophenyldi*-p-*tolylcarbinol* (VII*c*) was obtained similarly, in colourless crystals, m. p. 140° (yellow melt), from ethyl alcohol [Found: C, 73·5; H, 5·7; N, 3·1; S, 6·8; *M* (micro-Rast), 430. $C_{28}H_{27}O_3NS$ requires C, 73·5; H, 5·9; N, 3·1; S, 7·0%; *M*, 457]. It gives an yellow-orange colour with sulphuric acid.

(*c*) *Methylmagnesium iodide.* The dianthranilide (VI*b*) (1 g.) was treated with methylmagnesium iodide [from magnesium (0·6 g.), methyl iodide (3·6 g.), and dry ether (50 c.c.)] as described for (VII*b*). The oily residue was washed several times with light petroleum (b. p. 70—80°) and formed colourless crystals, m. p. 112° [Found: C, 62·8; H, 5·9; N, 4·4; S, 10·2; *M* (micro-Rast), 295. $C_{16}H_{19}O_3NS$ requires C, 62·9; H, 6·2; N, 4·6; S, 10·5%; *M*, 305]. 2-*Toluene*-p-*sulphonamidophenyldimethylcarbinol* (VII*d*) dissolves in cold aqueous sodium hydroxide and is recovered unchanged on acidification with dilute hydrochloric acid; it gives a yellow colour with sulphuric acid and is easily soluble in benzene and ethyl alcohol.

The carbinol (VII*b*) (1 g.) was refluxed with freshly distilled aniline (20 c.c.) for 3 hours. The mixture was then steam-distilled and the oily residue extracted with ether; the ethereal extract was dried (Na_2SO_4), evaporated, and the solid crystalline residue was recrystallised from benzene–light petroleum (b. p. 30—50°), forming colourless crystals, m. p. 212° (yellow melt). *Bis*-(2-*toluene*-p-*sulphonamidotriphenylmethyl*) *ether* is soluble in hot benzene and xylene, difficultly soluble in cold ethyl alcohol, benzene, and light petroleum (b. p. 30—50°); it gives a yellowish-brown colour with sulphuric acid [Found: C, 73·9; H, 4·9; N, 3·2; S, 7·5; *M* (micro-Rast), 795. $C_{52}H_{44}O_5N_2S_2$ requires C, 74·3; H, 5·2; N, 3·3; S, 7·6%; *M*, 840]. This ether was also obtained when the synthetic (VII*b*) was treated similarly (m. p. and mixed m. p.) (Found: C, 74·0; H, 5·1; N, 3·2; S, 7·4%).

Action of Aniline on NN′-*Ditoluene*-p-*sulphonyldianthranilide* (VI*b*).—The substance (Anschütz, *loc. cit.*) under exactly the same conditions afforded an oily residue, which after being washed several

times with light petroleum (b. p. 30—50°) and crystallised from benzene–light petroleum (b. p. 30—50°) formed colourless crystals, m. p. 140° [Found : C, 65·5; H, 4·8; N, 7·4; S, 8·4; *M* (micro-Rast), 360. $C_{20}H_{18}O_3N_2S$ requires C, 65·6; H, 4·9; N, 7·7; S, 8·8%; *M*, 366]. *2-Toluene-p-sulphonamidobenzanilide* is easily soluble in benzene and hot ethyl alcohol and difficultly soluble in light petroleum (b. p. 50—70°); it gives no colour when treated with concentrated sulphuric acid and reacts with ethereal diazomethane solution (details will be published later). The same substance was synthesised by interaction of a solution of 2-toluene-*p*-sulphonamidobenzoyl chloride (2 g.) (Anschütz, *loc. cit.*) in dry benzene (40 c.c.) and freshly distilled aniline (5 c.c.). The reaction mixture was refluxed for 4 hours, cooled, and filtered from the separated aniline hydrochloride. The benzene solution was washed with dilute hydrochloric acid, followed by aqueous sodium carbonate solution and then with water; it was dried (Na_2SO_4) and evaporated. The oily residue was washed several times with light petroleum (b. p. 50—70°) and the resulting solid crystallised from benzene–light petroleum (b. p. 30—50°) in colourless crystals identical (m. p. and mixed m. p.) with the foregoing (Found : C, 65·5; H, 4·9; N, 7·6; S, 8·5%).

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[*Received, April 29th,* 1948.]

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90. *Absorption Spectra and Structure of Organic Sulphur Compounds. Part I. Unsaturated Sulphides.*

By H. P. KOCH.

Ultraviolet absorption curves of various allyl, benzyl, acetyl, benzoyl, salicyl, phenyl, and nitrophenyl sulphides are presented and interpreted in terms of the most plausible polar excited structures deduced from the valency-bond resonance hypothesis. Hyperconjugation between C-S and C=C bonds is recognised in $\beta\gamma$-unsaturated sulphides, and first-order conjugation of lone-pair $3p^2$ sulphur electrons in $\alpha\beta$-unsaturated systems. The spectroscopic effect of crossed conjugation of a carbonyl group directly attached to both sulphur and an aromatic nucleus is exemplified by benzoyl and salicyl sulphides. A marked spectral variation which differentiates the isomeric 1- and 2-methyl*cyclo*hexyl phenyl sulphides is attributed to steric interference in the former molecule forbidding the geometrical conditions required for effective conjugation between sulphur and the benzene ring. Quasi-conjugation of the two aromatic rings appears to take place in diphenyl sulphide. Both steric and electronic interaction effects between non-bonded groups are invoked to account for the unusual chromophoric properties of phenyl *o*-nitrophenyl sulphide and related compounds.

ALTHOUGH considerable progress has recently been made in the chemistry of organic sulphur compounds, mainly in relation to substances exhibiting anti-bacterial activity and in connection with the study of rubber vulcanisation, the reactivity of such molecules is still very imperfectly understood. The nature of electronic interaction between sulphur atoms and other functional groups requires much further elucidation. At the same time, the molecular structure of some important types of compound such as the polysulphides has not so far been established with any certainty.

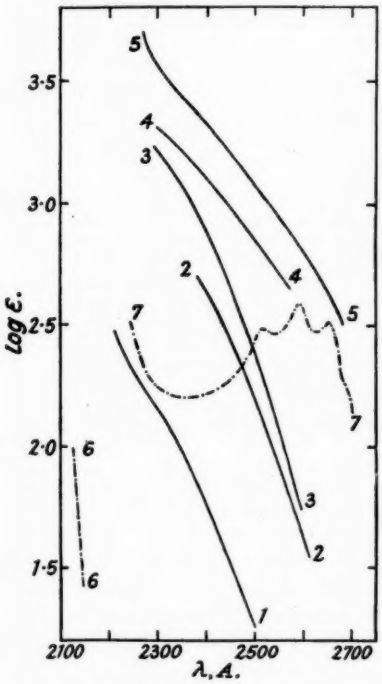
Clearly, the final solution of such problems must await the application of rigorous wave-mechanical treatment on one hand and of *X*-ray structure analysis on the other, but in view of the rather intractable nature of these methods when applied to complex systems of a low degree of symmetry, it was thought worth while to explore the field by means of a more empirical approach. The ultraviolet absorption spectra in solution of a considerable variety of sulphur-containing molecules have therefore been examined, and the present series of papers is largely concerned with an attempt at correlation over a very extensive field. Although some of the results must necessarily be regarded as tentative, they will nevertheless suggest a number of useful points of attack for future work, and definitive conclusions about organic structure can often be deduced from the ultraviolet data. Further justification of the semi-empirical study of absorption spectra may be derived from the intrinsic value of the new experimental material which is thereby placed on record, be it for purposes of characterisation and chemical analysis or with regard to current theories of light absorption.

In absorbing ultraviolet rays of wave-lengths greater than 2000 A., a molecule passes from the ground state to an upper excited electronic level, and the frequency of the radiation absorbed is characteristic of the energy difference involved. Much of the subsequent discussion will be presented in terms of the commonly accepted working hypothesis that the excited state resulting from high-intensity absorption of light contains a significant proportion of polar structures in the resonance hybrid, and that the direction of polarisation in the excited structure is more or less parallel to the direction of the electric vector of the light absorbed. The postulated excited polar canonical structures will be chosen in accordance with the general rules that they should be energetically plausible, self-consistent over the entire field of sulphur compounds under

investigation, compatible with the geometrical arrangement of the atoms in the molecule, and also as far as possible in agreement with the nature of the bonds as inferred from independent physical and chemical evidence. In the latter connection, reference will be made to *X*-ray and electron-diffraction data, vibrational spectra, and reactivity behaviour, wherever such information is available.

Saturated Dialkyl Sulphides.—The ultraviolet absorption spectra of dialkyl sulphides have hitherto been investigated mainly by Ley and Arends (*Z. physikal. Chem.*, 1932, *B*, **15**, 311) and by Sjöberg (*ibid.*, 1942, **52**, 209), who reported the occurrence of a characteristic maximum at 1960 A., preceded by a low-intensity inflection near 2300 A. The former absorption region falls outside the range of the conventional quartz spectrophotometer employed in the present work, but the inflection is indicated in the absorption curve of di-*n*-butyl sulphide which is reproduced in Fig. 1.

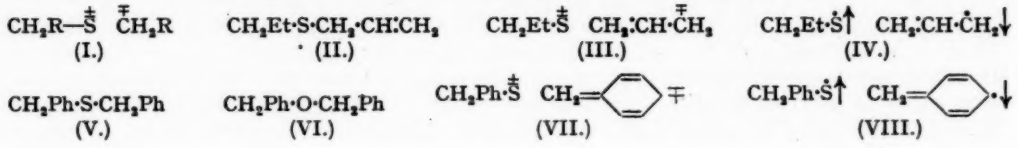
FIG. 1.



1. *Di*-n-*butyl sulphide.*
2. *Propyl allyl sulphide.*
3. *Diallyl sulphide.*
4. *Di*cyclo*hex-2-enyl sulphide.*
5. *Dibenzyl sulphide.*
6. cyclo*Hexene* (*in* C_6H_{12}).
7. *Dibenzyl ether* (*in* C_6H_{12}).

No interpretation of this dialkyl sulphide spectrum has hitherto been advanced. In view of the relatively high intensity of the absorption peak at 1960 A. ($\log \varepsilon > 3$), it seems likely that charge-transfer rather than a purely intra-atomic valency shell transition is involved (cf. Mulliken, *J. Chem. Physics*, 1939, **7**, 135), so that the excited state may be considered to contain a significant proportion of the polar structures (I). Such excitation involves the polarisation of the p–sp^3 bond between sulphur and carbon, and the charge may presumably be transferred in either direction in view of the equivalence of these two atoms on the electronegativity scale given by Pauling (" The Nature of the Chemical Bond ", p. 60).

βγ-Unsaturated Sulphides.—The absorption properties of allyl and benzyl sulphides differ markedly from those of saturated dialkyl sulphides, but in a manner to be expected from the above hypothesis of polarisation of the sulphur–carbon bond in the excited structure (I). Curves 1, 2, and 6 of Fig. 1 demonstrate that propyl allyl sulphide (II) absorbs much more strongly and at longer waves than the sum of the separate absorptions of a saturated sulphide and a typical olefin, although sulphur and double bond are chromophorically insulated by the saturated methylene group in this molecule. Some kind of electronic interaction is evidently taking place, and the energy of the excited state has become lowered relative to that of the ground state. This phenomenon may be readily accounted for by a combination of the previously postulated structure (I) with the well-known principle of allylic resonance. In propyl allyl sulphide the first excited state would be expected to become stabilised by additional resonance contributions from the structures (III), resulting in the observed red shift of the ultraviolet absorption spectrum. Similar and yet more marked effects occur in diallyl sulphide (curve 3) and in the secondary βγ-unsaturated di*cyclo*hexenyl derivative (curve 4). Again, the absorption properties of dibenzyl sulphide (V; curve 5) may be contrasted with those of the homologous oxide (VI; curve 7) which has been examined by Mayer-Pitsch (*Z. Elektrochem.*, 1943, **49**, 368). The dibenzyl ether spectrum is " normal " in its close resemblance to the absorption of two chromophorically insulated alkylbenzene systems, but dibenzyl sulphide absorbs much more strongly with complete masking of the aromatic fine-structure bands. It is suggested that canonical structures of the polar (*o*- or *p*-) quinonoid type (VII) make a significant contribution to the optically excited state.



Some interesting support for the above ideas may be obtained from chemical and infra-red data which suggest that excited structures similar to (III) and (VII), possibly of the formal-bonded type (IV) and (VIII), may be of some importance in reactivity phenomena and even in the ground state of the molecule. Thus, Dr. Norman Sheppard (private communication) has observed that the S–C stretching vibration occurs at much lower frequencies in allyl that in saturated sulphides, and a similar effect is implicit in the data of Trotter and Thompson on benzyl and other disulphides (*J.*, 1946, 481; see following paper). These low-vibration frequencies are almost certainly indicative of a reduction in the physical strength of the sulphur–carbon bonds compared with those of the saturated analogues. Again, the relative chemical instability of the S–C linkage in βγ-unsaturated sulphides is apparent in the rather facile decomposition of dibenzyl sulphide on heating or in the presence of alkali (Hinsberg, *Ber.*, 1931, **64**, 2500), in the bond fission which occurs on reaction of diallyl sulphide with methyl iodide (Selker and Kemp, *Ind. Eng. Chem.*, 1944, **36**, 16), and in the equally characteristic reductive scission undergone by allylic but not by saturated sulphides in the presence of nascent hydrogen (Farmer and Shipley, *J. Polymer Sci.*, 1946, **1**, 300).

Clearly the ultraviolet, infra-red, and chemical evidence all seems to lead to the same general conclusion that a process akin to hyperconjugation takes place in the system C=C—C—S. Similar hyperconjugation has long been recognised in α-methylenic olefins, C=C—C—H (cf. Deasy, *Chem. Reviews*, 1945, **36**, 145), and recently also in allylic halides, C=C—C—Hal (Baker, *Trans. Faraday Soc.*, 1941, **37**, 635; De la Mare, Hughes, and Ingold, *J.*, 1948, 17).

αβ-*Unsaturated Sulphides.*—It is well known that when an atom such as chlorine or nitrogen is directly attached to a carbon–carbon double bond, conjugation occurs between the unsaturated grouping and a lone pair of non-bonding *p*-electrons on the hetero-atom (cf. Walsh, *Trans. Faraday Soc.*, 1945, **41**, 35; Bowden, Braude, Jones, and Weedon, *J.*, 1946, 45). The lone pair of $3p^2$ electrons in the outer valency shell of the sulphur atom displays analogous conjugating properties in αβ-unsaturated suphides, exemplified by such phenomena as the aromatic character of thiophen (Pauling, *op. cit.*, p. 226) or the low dipole moment of divinyl sulphide (IX) which is attributable to resonating polar structures of type (X) (Hannay and Smyth, *J. Amer. Chem. Soc.*, 1946, **68**, 1005). As would be expected from such first-order conjugation, αβ-unsaturated sulphides absorb much more strongly in the ultraviolet than either the saturated or the hyper-conjugated βγ-unsaturated compounds. For instance, divinyl sulphide is reported to exhibit an absorption maximum of $\varepsilon = 5000$ near 2550 A. (Mohler, *Helv. Chim. Acta*, 1940, **23**, 1200), and 2-chloroethyl vinyl sulphide gives rise to a strong band at 2280 A. ($\varepsilon = 7000$) according to Bowden, Braude, and Jones (*J.*, 1946, 948). Vinyl sulphides, however, are not easily accessible in a state of high purity, and in the present paper a detailed account will be given of the spectra of phenyl and of α-carbonyl sulphides as interesting examples of this type of conjugation.

According to the views independently put forward by Kimball (*J. Chem. Physics*, 1940, **8**, 188) and by Rothstein (*J.*, 1940, 1550), an electron pair may be donated to one of the unfilled 3*d* orbitals of the sulphur atom. It is therefore possible that oppositely charged structures (X*a*) might also make some contribution to the excited states of vinyl and phenyl sulphides.

(IX.) $CH_2{:}CH{\cdot}\ddot{S}{-}CH{:}CH_2$ (X.) $CH_2{:}CH{\cdot}\overset{+}{\ddot{S}}{:}CH{\cdot}C\bar{H}_2$ (X*a*.) $CH_2{:}CH{\cdot}\bar{\ddot{S}}{:}CH{\cdot}\overset{+}{C}H_2$

Acetyl Sulphides.—The ultraviolet absorption properties of a number of simple acetyl sulphides of the general formula (XI) have already been examined in alcoholic solution by Sjöberg (*loc. cit.*), who observed characteristic high-intensity maxima (log ε 3·56—3·60) near 2300 A. A similar band is also given by acetyl *cyclo*hexyl sulphide (XII; $R' = C_6H_{11}$) in *cyclo*hexane solution ($\varepsilon = 4500$ at 2315 A.; curve 1 of Fig. 2), and this spectrum is undoubtedly associated with the sulphur–carbonyl conjugation involving contributions from the polar canonical structure (XIII) in the excited state.

Progressive red shifts are displayed on stepwise replacement of the three hydrogen atoms of the acetyl group by chlorine. Thus, chloroacetyl *cyclo*hexyl sulphide absorbs maximally at 2380 A., the dichloroacetyl derivative at 2495 A., and the trichloro-compound at 2545 A., although no corresponding increases are noted in the intensity of the absorption (cf. Fig. 3). It seems likely that the explanation of these halogenation red shifts is to be sought in a raising of the ground state relative to the excited state, rather than in any change in the latter. Similar inductive or charge-transfer effects of chlorine transmitted through one saturated carbon atom are well known to affect the ground state of the related chloroacetic acids (XIV).

$CH_2R{-}\ddot{S}{-}CO{\cdot}CH_2$ (XI.) $R'{-}\ddot{S}{-}CO{\cdot}CH_2$ (XII.) $R'{-}\overset{+}{\ddot{S}}{=}C\bar{O}{-}CH_2$ (XIII.) $H{-}O{-}CO{-}CH_2Cl$ (XIV.)

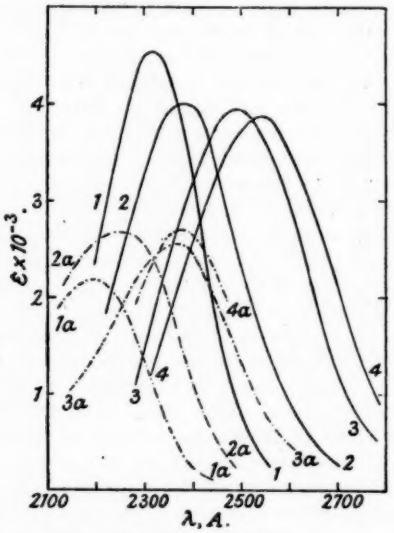
C C

The broken curves of Fig. 2 illustrate the spectra of the acetyl hydrogen sulphides (thiolacetic acids; XII, R′ = H) corresponding to the above *cyclo*hexyl-substituted compounds. Infra-red absorption and other physical data confirm the acetyl–thiol structure of thiolacetic acid itself, and the curves show that the ultraviolet spectra of all four acids are of the same general type as those of their alkyl derivatives, although both wave-length and intensity of the bands have become considerably reduced. Electron-diffraction bond-length measurements due to Gordy (*J. Chem. Physics*, 1946, **14**, 560) suggest that the polar structure (XIII; R′ = H) makes only a very slight contribution to the ground state of thiolacetic acid.

It has previously been reported from these laboratories (Cunneen, *J.*, 1947, 137) that variation of the nature of the alkyl substituent has no influence on the acetyl sulphide spectrum, *cyclo*hexyl, 2-methyl*cyclo*hexyl, dihydromyrcene, and rubber acetyl sulphides being virtually identical in this respect.

FIG. 2.

Acetyl sulphides (in C_6H_{12}).

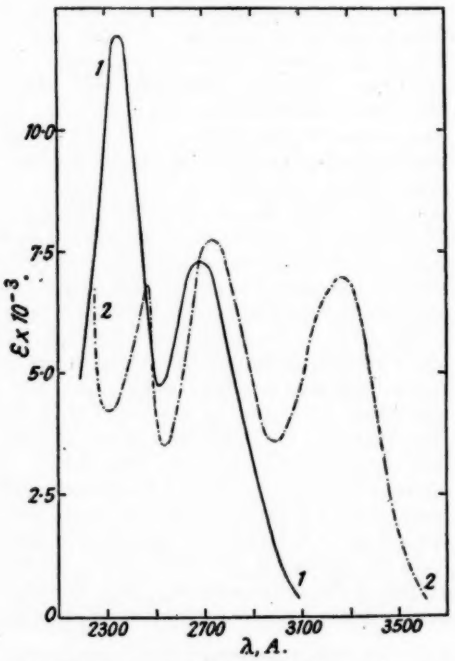


1. *Acetyl* cyclo*hexyl sulphide.*
2. *Monochloroacetyl* cyclo*hexyl sulphide.*
3. *Dichloroacetyl* cyclo*hexyl sulphide.*
4. *Trichloroacetyl* cyclo*hexyl sulphide.*

1*a*. *Thiolacetic acid.*
2*a*. *Monochlorothiolacetic acid.*
3*a*. *Dichlorothiolacetic acid.*
4*a*. *Trichlorothiolacetic acid.*

FIG. 3.

Benzoyl sulphides (in C_6H_{12}).

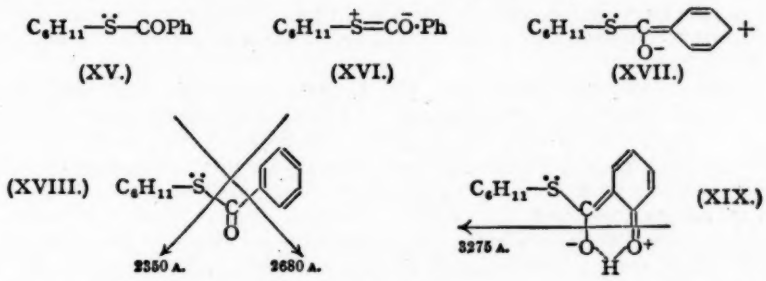


1. *Benzoyl* cyclo*hexyl sulphide.*
2. o-*Hydroxybenzoyl* cyclo*hexyl sulphide.*

Benzoyl and Salicyl Sulphides.—The molecule of benzoyl *cyclo*hexyl sulphide (XV) contains a system of crossed conjugation. Two alternative polar excited structures are reasonable, in which the oxygen acquires negative charge either from the sulphur atom (XVI) or from the benzene ring (XVII; *p*- or *o*-quinonoid). The observed ultraviolet spectral characteristics strongly suggest that both types of excitation take place independently of each other on absorption of light (curve 1 of Fig. 3). The first band at 2680 A. ($\varepsilon = 7300$) greatly resembles the analogous maxima of the series of acetyl sulphides, except for a further red shift which may be attributed to the ground-state effect of phenyl substitution. On the other hand, the more intense maximum at 2350 A. ($\varepsilon = 12{,}000$) coincides with the absorption displayed by an isolated benzoyl group in such molecules as acetophenone or dibenzoyl peroxide. Thus, the two absorption regions of benzoyl *cyclo*hexyl sulphide appear to correspond to two distinct modes of electronic transition, one (at 2680 A.) proceeding to an excited state containing a high proportion of the polar form (XVI), and the other (at 2350 A.) to an upper level involving the quinonoid structures (XVII). These two types of excitation occurring in the same molecule preserve their independent identity presumably because they are associated with electric moments approximately at right angles to each other in the plane of the conjugated system. For a given molecule (XVIII) at any given

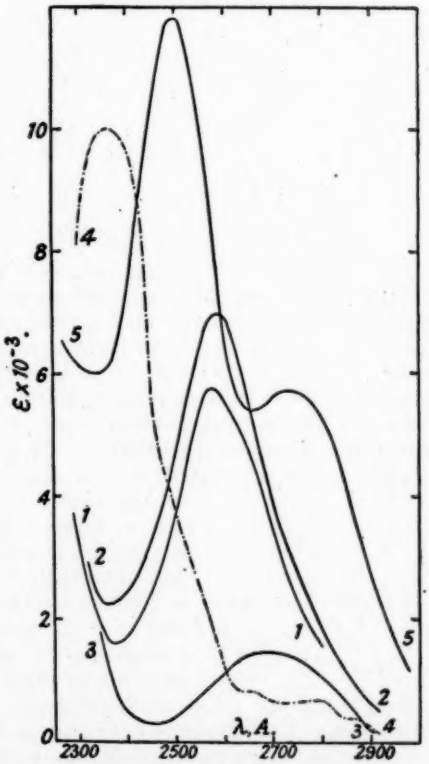
instant, the main absorption may be visualised as taking place *either* at 2680 A. *or* at 2350 A., depending on the orientation of the molecule relative to the electric vector of the incident light. Other analogous systems of crossed conjugation will be discussed in Part III.

When a hydroxyl group is substituted in the *o*-position of the benzoyl sulphide molecule, further interesting spectral changes occur (curve 2, Fig. 3). The 2680 A. sulphur conjugation



band is only slightly changed (maximum at 2745 A., $\varepsilon = 7700$), but the integrated area of the benzoyl absorption has been greatly reduced ($\varepsilon = 6700$ at 2475 A.) while there emerges a new long-wave band at 3275 A. ($\varepsilon = 7000$). The latter wave-length position is characteristic of the salicyl group (Morton and Stubbs, *J.*, 1940, 1354), and the new band is doubtless associated with the polar excited structure (XIX), utilising the electron-donor properties of the phenolic oxygen. The electric moment of this transition should be expected to be inclined at some 45° to that of the benzoyl type of excitation, and it seems to " steal " most of the intensity of the latter.

FIG. 4.
Phenyl sulphides.



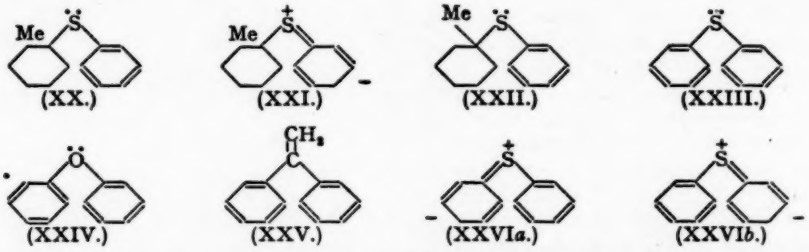
1. cyclo*Hexyl phenyl sulphide* (*in* C_6H_{12}).
2. 2-*Methyl*cyclo*hexyl phenyl sulphide* (*in* C_6H_{12}).
3. 1-*Methyl*cyclo*hexyl phenyl sulphide* (*in* C_6H_{12}).
4. *Thiophenol* (*in* C_6H_{12}).
5. *Diphenyl sulphide* (*in* EtOH).

Phenyl Sulphides.—The broken curve 4 of Fig. 4 represents the spectrum of thoiphenol, in good accord with similar measurements by Chaix (*Bull. Soc. chim.*, 1933, **53**, 700), Böhme and Wagner (*Ber.*, 1942, **75**, 606), and Bowden, Braude, and Jones (*loc. cit.*). The relatively weak and discontinuous first absorption region from 2950 to 2600 A. is no doubt due to the partial benzenoid chromophore, while the intense band at 2360 A. must be assigned to first-order conjugation between the non-bonding ($3p^2$) electron pair of the sulphur atom and the π-electrons of the benzene ring. Curves 1 and 2 indicate that alkylation of the acidic hydrogen induces a marked red shift of this absorption, similar to that observed with thiolacetic acid, although the extinction coefficient is here reduced rather than intensified.

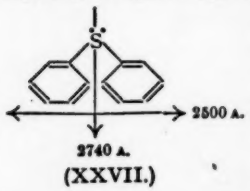
A remarkable variation arises between the spectral curves 2 and 3 which differentiate the isomeric 1-methyl- and 2-methyl-*cyclo*hexyl phenyl sulphides (cf. Cunneen, *J.*, 1947, 36). In accordance with normal expectation, the 2-methyl isomer (XX) resembles the non-methylated *cyclo*hexyl compound in displaying a strong band at 2590 A. ($\varepsilon = 7000$), attributable to excitation involving the plausible polar resonance structures (XXI; *p*- or *o*-quinonoid); but little more than the residual aromatic absorption occurs when the methyl substituent is placed in the 1-position (XXII). The explanation of this anomaly is to be sought in steric factors. The

symmetry properties of the sulphur *p*-orbitals require that in the polar excited form (XXI) the sulphur–*cyclo*hexyl single bond should lie in the same plane as the benzene ring, a condition which cannot be fulfilled in the molecule of 1-methyl*cyclo*hexyl phenyl sulphide (XXII) because of steric hindrance. Scale models of the latter isomer suggest that considerable spatial interference occurs between an aromatic *o*-hydrogen and one of the groups attached to the quaternary carbon atom as long as the sulphur–*cyclo*hexyl bond is kept coplanar with the benzene ring. The polar resonance form analogous to (XXI) would therefore be highly unstable in the 1-methyl compound (XXII), a circumstance which brings about the disappearance of the characteristic ultraviolet absorption.

Diphenyl sulphide (XXIII; curve 5 of Fig. 4) gives rise to two high-intensity absorption bands, at 2740 A. ($\varepsilon = 5700$) and at 2500 A. ($\varepsilon = 11{,}800$), in agreement with those recorded by Chaix (*loc. cit.*). The 2740 A. absorption no doubt corresponds to the 2575 A. sulphur–benzene conjugation band of *cyclo*hexyl phenyl sulphide which is of similar intensity, the red shift being attributable at least in part to a change in the energy of the ground state. As regards the new and very strong maximum at 2500 A., comparison with the spectra of related molecules suggests that the associated upper electronic state may involve the resonance of charge between the two aromatic rings which are quasi-conjugated *via* the non-bonding 3*p* orbital of the intervening sulphur atom. Similarly intense ultraviolet absorption has been observed in the 2000—2500 A. region of diphenyl ether (XXIV) (Mayer-Pitsch, *loc. cit.*) and *as*-diphenylethylene (XXV) (Jones, *J. Amer. Chem. Soc.*, 1943, **65**, 1818). In terms of the conventional valency-bond formulæ, the postulated excited level contains important contributions from a resonance hybrid of the equivalent structures (XXVI, *a* and *b*).



The apparently independent existence of two alternative modes of conjugation and electronic excitation in the diphenyl sulphide molecule may conceivably be ascribed to the fact that a considerable energy barrier arising from the steric interference of two *o*-hydrogen atoms must oppose the coplanar configuration demanded by the resonance (XXVI *a* and *b*) (cf. Coates and Sutton, *J.*, 1942, 567; Jones, *loc. cit.*). Rotation of one of the benzene rings out of the common plane would leave the sulphur conjugation of the other benzene ring unimpaired (absorption at 2740 A.), or, alternatively, a lesser degree of rotation and partial conjugation of *both* benzene rings might occur (absorption at 2500 A). In the crystal structure of the *pp'*-dibromo-derivative of diphenyl sulphide (Toussaint, *Bull. Soc. chim. Belg.*, 1945, **54**, 319) both benzene rings are symmetrically inclined at 36° to their hypothetical common plane, and a similar symmetrical structure would seem to be the most likely configuration of the ground state of diphenyl sulphide in solution. More probably, then, the real reason why the two closely interrelated types of conjugation can be recognised as separate entities absorbing at 2740 and 2500 A., respectively, arises from the circumstance that the two transitions are associated with electric moments approximately at right angles to each other in the near-planar structure (XXVII). For a given molecule, the relative absorption at the two alternative wave-length positions will then be a function of the molecular orientation relative to the electric vector of the incident light.



(XXVII.)

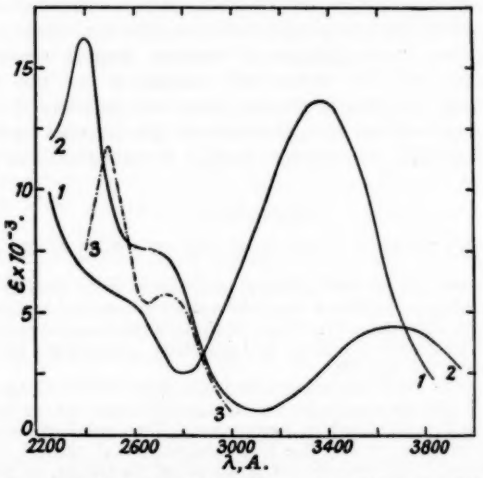
Bromo- and Nitro-phenyl Sulphides.—The *pp'*-dibromodiphenyl sulphide described crystallographically by Toussaint (*loc. cit.*) was also examined in the present spectroscopic survey. The absorption bands in solution are of the same general character as those displayed by the halogen-free parent compound, but the whole spectrum is displaced in the direction of longer wave-lengths and greater intensities. Thus, the 2500 A. ($\varepsilon = 12{,}000$) band of diphenyl sulphide is shifted to 2580 A. ($\varepsilon = 19{,}000$), and the 2740 A. ($\varepsilon = 6000$) band to 2820 A. ($\varepsilon = 9500$) on *pp'*-bromination. Both ground and excited states are probably affected by the inductive electronegative influence of halogen substitution, but the energy difference between the two levels has clearly been

reduced and the transition moment enhanced. Analogous spectral displacement occurs on *p*-bromination of dimethylaniline (Remington, *J. Amer. Chem. Soc.*, 1945, **67**, 1838).

Some interesting effects are observed when a single nitro-group is introduced in the *p*- or *o*-position of diphenyl sulphide (XXVIII and XXXI). Toussaint (*Bull. Soc. roy. Sci. Liége*, 1943, 533) noted that the *o*- but not the *p*-isomer absorbed radiation at 4360 A. and was the more deeply coloured. Whereas the *o*-isomer exhibits high-intensity absorption resembling that of unsubstituted diphenyl sulphide, Fig. 5 shows that the total near-ultraviolet absorption of the *p*-compound is actually very much greater than that of the *o*-form, although at *shorter* wavelengths (below 2900 A.) the *p*-derivative is more transparent. Analogous relationships characterise the spectra of the *p*- and *o*-nitrodimethylanilines which afford the same type of lone-pair electron conjugation, with basic nitrogen substituted for sulphur (cf. Remington, *loc.*

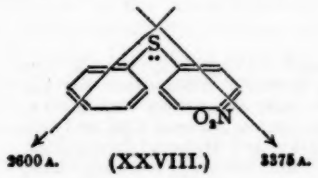
FIG. 5.

Nitrophenyl sulphides (*in* EtOH).

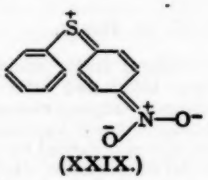


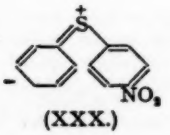
1. *Phenyl* p-*nitrophenyl sulphide.* 3. *Diphenyl sulphide.*
2. *Phenyl* o-*nitrophenyl sulphide.*

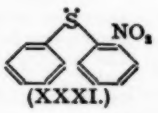
cit.). As regards the *p*-isomers, comparatively stable polar excited structures such as (XXIX) may be written, and nitro-group conjugation of this type is doubtless responsible for the intense absorption band of phenyl *p*-nitrophenyl sulphide at 3375 A. ($\varepsilon = 13{,}500$) (curve 1 of Fig. 5). The inflection near 2600 A. may be attributed to alternative polarisation by electric vectors oriented at right angles to the above, involving the sulphur conjugation of the unsubstituted aromatic ring (*o*- and *p*-quinonoid polar structures XXX). In the *o*-nitrated molecule (XXXI),

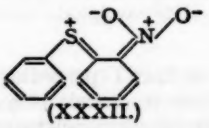


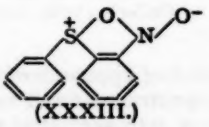
(XXVIII.)

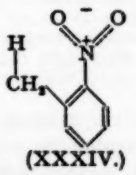

(XXIX.)

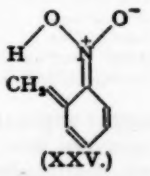

(XXX.)


(XXXI.)


(XXXII.)


(XXXIII.)


(XXXIV.)


(XXV.)

the main axes of polarisation would be expected to be directed differently from those of the *p*-isomer, and curves 2 and 3 demonstrate that below 3000 A. the spectrum is remarkably like that of the unsubstituted diphenyl sulphide. In fact, the spectroscopic effect of the *o*-nitro-group

is relatively slight, and the long-wave absorption attributable to nitro-group conjugation (XXXII) is greatly reduced in intensity. Steric hindrance may again be recognised. The postulated polar excited structure (XXXII) demands the nitro-group to be coplanar with the benzene ring, a condition which is improbable or energetically disfavoured because of the resulting interference between the van der Waals radii of one of the oxygens and the sulphur atom (cf. Hampson *et al.*, *J.*, 1937, 10; 1939, 98; Thomson, *J.*, 1944, 404; Remington, *loc. cit.*). Hence the reduced intensity of the characteristic maximum. Generally, short-wave displacement accompanies the intensity decrease of sterically hindered conjugation bands, and the observed *red* shift of the near-ultraviolet absorption relative to that of the *p*-isomer seems anomalous. Similar unusual red-shifts were also reported by Remington (*loc. cit.*) for the hindered *o*-nitroanilines which were more deeply coloured than the unhindered *p*-isomers, but no explanation was then offered. It is now suggested that these peculiarities may arise from some degree of electronic interaction across space between the two non-bonded interfering groups. In terms of extreme canonical resonance structures, the polar excited state of phenyl *o*-nitrophenyl sulphide is thought to be stabilised by minor contributions from the cyclic form (XXXIII), which seems both sterically and energetically reasonable. Rather similarly, the hindered conjugation between nitro-group and benzene ring in *o*-nitrotoluene (XXXIV; cf. Remington, *loc. cit.*) may well be somewhat stabilised by the hydrogen bonding and hyperconjugation phenomena implied in the hypothetical extreme structure (XXXV). These formulations offer at least a qualitative explanation of the unusual wave-length positions in the sterically hindered low-intensity absorption bands of *o*-nitro-substituted phenyl sulphides, anilines, and toluenes.

Experimental.

The absorption curves were recorded in the usual manner with a Hilger small quartz spectrograph and Spekker photometer.

Diphenyl sulphide and the alkyl and alkenyl sulphides were prepared and purified in these laboratories by Dr. F. W. Shipley. Dibenzyl sulphide was a commercial sample which melted at 48—49° after recrystallisation. The bromo- and nitro-phenyl sulphides were made available through the kindness of Dr. J. Toussaint of the University of Liége, and all other compounds described in this paper were furnished by Dr. J. I. Cunneen (cf. *loc. cit.*).

Beer's law was obeyed by the dilute spectrographic solutions of the thiolacetic acids in *cyclo*hexane.

Independently prepared duplicate solution were examined for each of the three phenyl alkyl sulphides described, and concordant results obtained in every case. The small difference observed between the absorption intensities of the *cyclo*hexyl and the 2-methyl*cyclo*hexyl phenyl sulphides therefore appears to be significant. On the other hand, the 2590 A. absorption maximum of the phenyl sulphide derived from dihydromyrcene (Cunneen, *loc. cit.*) coincides exactly with that of the analogously alkyl-substituted 2-methyl*cyclo*hexyl compound.

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91. *Absorption Spectra and Structure of Organic Sulphur Compounds. Part II. Disulphides and Polysulphides.*

By H. P. Koch.

Existing physical data point to a stabilised static non-planar configuration of the two valencies attached to the sulphur–sulphur bond and offer a possible explanation for the anomalous failure of di-*tert.*-butyl disulphide to display characteristic absorption near 2500 A. The spectra of diallyl and dibenzyl disulphides suggest hyperconjugation between C=C and C–S bonds (cf. Part I). Ultraviolet-absorption curves obtained for dialkyl and diphenyl disulphides, sulphur, thionyl chloride, sulphur mono- and di-chlorides, dialkyl and diphenyl tetrasulphides, two representative thiokols, and a dialkyl hexasulphide provide strong evidence in favour of the straight-chain formulation of polysulphide structure. The resonance properties and reactivities of S–S bonds in their dependence on intramolecular environment are discussed. Some reserve is expressed with regard to Fuller's cyclic structure of tetrasulphide thiokols incorporating co-ordinately linked sulphur.

By further application of the general method of approach outlined in Part I (preceding paper), it is proposed now to consider the molecular structure and some of the resonance properties of organic disulphides and polysulphides. A representative number of ultraviolet-absorption spectra have been obtained, and these will be discussed together with such related structural information as is obtainable from other physical and chemical data in the field.

Saturated Dialkyl Disulphides.—The straight-chain bond-structure of hydrogen disulphide,

dimethyl disulphide, and dichlorine disulphide (sulphur monochloride) has been established by Raman spectra and electron-diffraction investigations (Palmer, *J. Amer. Chem. Soc.*, 1938, **60**, 2360; Stevenson and Beach, *ibid.*, p. 2872; Feher and Baudler, *Z. Elektrochem.*, 1941, **47**, 844), and no evidence has hitherto come to light in support of the possible existence of structural isomers of the branched-chain type containing a co-ordinated sulphur atom in the side chain. The chemical properties of organic disulphides are also in full accord with the "linear" formulation analogous to the structure of organic peroxides. Direct information regarding the possibility or otherwise of free rotation about the S–S bonds in simple dialkyl disulphide molecules is lacking. Penney and Sutherland (*Trans. Faraday Soc.*, 1934, **30**, 898) have, however, shown theoretically that interaction of the unsymmetrical electron clouds of two oxygen or nitrogen atoms should stabilise a non-planar skew arrangement of groups about the O–O or N–N linkages in hydrogen peroxide and hydrazine, and similar considerations presumably apply to the disulphide bond. In confirmation of these ideas, Zumwalt and Giguère (*J. Chem. Physics*, 1941, **9**, 458) obtained evidence for the static non-planar character of the hydrogen peroxide molecule from infra-red analysis, and exact correspondence has been noted between the Raman frequencies of this molecule and its sulphur analogue, hydrogen disulphide (Feher and Baudler, *loc. cit.*). Analogous non-planar configurations of the two structures may therefore be regarded as highly probable. The observed azimuthal angle between the two hydroxyl groups in hydrogen peroxide is about 105° (cf. model shown in *Ann. Reports*, 1942, **39**, 104), and virtually identical azimuthal angles around the S–S linkages have recently been found in the accurately determined structures of *pp'*-dibromodiphenyl disulphide, dimethyl trisulphide, and elementary sulphur (see below). Thus, all the available evidence suggests that a non-planar and almost right-angled skew distribution of valencies about the sulphur–sulphur bond is energetically preferred.

The ultraviolet absorption of saturated organic disulphides is characterised by a relatively weak and rather broad maximum near 2500 A., together with intense absorption near the edge of the quartz-ultraviolet region. These general features are illustrated by the spectra of di*iso*amyl and di*cyclo*hexyl disulphides recorded in Fig. 1, as well as by the previously reported diethyl disulphide spectrum (Ley and Arends, *Z. physikal. Chem.*, 1932, *B*, **15**, 311), the cysteine absorption curve due to Anslow and Lyman (*J. Opt. Soc. Amer.*, 1941, **31**, 114), and the absorption of disulphide thiokol (see below). It seems rather remarkable, then, that no selective absorption near 2500 A. should be displayed by di-*tert.*-butyl disulphide (curve 3, Fig. 1). In view of the entirely normal spectral properties of the di*cyclo*hexyl derivative containing sulphur linked to a secondary carbon atom, the anomalous behaviour of the *tert.*-butyl compound appears to be associated with steric rather than inductive electronic effects. If, in fact, the 2500 A. absorption region is in some way related to the electron-cloud interaction responsible for the energetically preferred skew configuration of disulphides, then the suppression of this absorption in di-*tert.*-butyl disulphide would be expected as a result of steric hindrance. Scale models indicate that spatial interference between the two *tert.*-butyl groups would strongly militate against the conformation of the disulphide valencies at an azimuthal angle near 100°.

It was suggested in the preceding paper that polar excited structures of the type (I) are important in the intense absorption of saturated dialkyl monosulphides near 2000 A. If this hypothesis is correct, similar polarisation of both C–S and presumably even more markedly of S–S bonds (II) should arise in the analogous high-intensity short-wave absorption of dialkyl disulphides. Independent evidence of the relative weakness or polarisability of the covalent disulphide linkage is probably provided by its propensity for symmetrical radical dissociation (Waters, *Trans. Faraday Soc.*, 1946, **42**, 189), and by the well-known facile hydrative fission observed in the presence of alkali. It will also appear below that the concept of partial ionic bond character affords a satisfactory explanation of the interesting conjugation phenomena arising in aromatic disulphides and in polysulphides.

$$CH_3R{-}\overset{\pm}{\underset{\cdot\cdot}{S}}\,|\,\overset{\mp}{C}H_2R \qquad\qquad CH_3R{-}\overset{\pm}{\underset{\cdot\cdot}{S}}\;\overset{\mp}{\underset{\cdot\cdot}{S}}{-}CH_2R$$

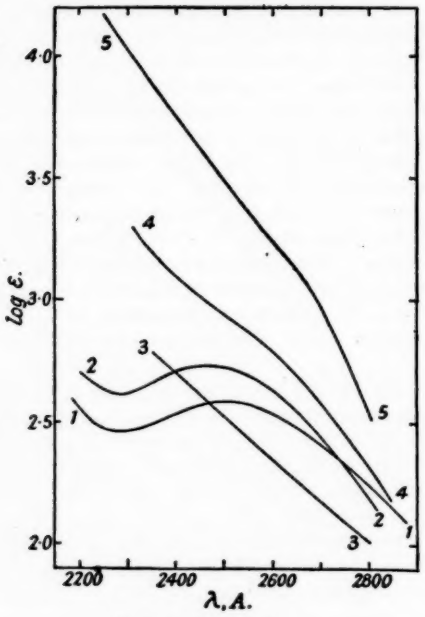
(I.) (II.)

βγ-Unsaturated Disulphides.—The absorption curve of diallyl disulphide (III; curve 4, Fig. 1) exhibits an inflection near 2450 A. which probably corresponds to the characteristic 2500 A. region of saturated disulphides, but this has now become merged into the increased absorption displayed by all allylic sulphide groupings (cf. this vol., p. 388). According to resonance theory, the polar excited level (I) should be stabilised in the βγ-unsaturated compounds because of allylic resonance of the formal charge on the carbon atom, and this circumstance

would result in the observed red shift and enhancement of the absorption. Thus, both (IV) and (V) probably contribute to the excited states associated with the observed ultraviolet-absorption properties of diallyl disulphide (III). With regard to the postulated hyperconjugated form (IV), which implies fractional bond order for the C–S linkage, it may well be significant that the bond in question is chemically weaker in allylic than in saturated disulphides (Bloomfield, private communication).

FIG. 1.

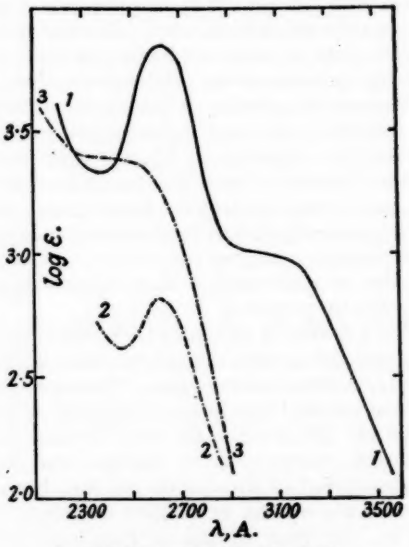
Dialkyl disulphides, R·S_2·R (*in* EtOH).



1. R = iso*Amyl*.
2. R = cyclo*Hexyl*.
3. R = tert.-*Butyl*.
4. R = *Allyl*.
5. R = *Benzyl*.

FIG. 2.

Sulphur chlorides (*in* n-*hexane*).



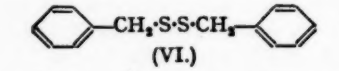
1. *Sulphur monochloride*, S_2Cl_2.
3. *Thionyl chloride*, $SOCl_2$.
2. *Sulphur dichloride*, SCl_2.

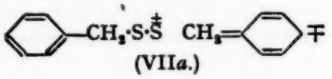
Analogous hyperconjugation in the corresponding $\beta\gamma$-unsaturated dibenzyl disulphide molecule (VI) may be deduced from the strong and general ultraviolet extinction recorded as curve 5 of Fig. 1. This absorption is even greater than that of the related monosulphide (see

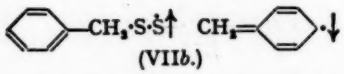
$CH_2{:}CH{\cdot}CH_2{\cdot}S{\cdot}S{\cdot}CH_2{\cdot}CH{:}CH_2$ (III.)

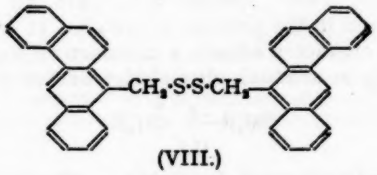
$CH_2{:}CH{\cdot}CH_2{\cdot}S{\overset{+}{\cdot}}\overset{\ddots}{S}\ CH_2{:}\overset{\mp}{C}H{\cdot}CH_2$ (IV.)

$CH_2{:}CH{\cdot}CH_2{\overset{+}{\cdot}}\overset{\ddots}{S}\ \overset{\mp}{S}{\cdot}CH_2{\cdot}CH{:}CH_2$ (V.)


(VI.)


(VIIa.)


(VIIb.)


(VIII.)

Part I) which it otherwise resembles in the complete masking of fine-structure aromatic bands. Again, Trotter and Thompson (*J.*, 1946, 481) found that the characteristic stretching-frequency of the C–S bond was lowered from 631 cm.$^{-1}$ in dipropyl to 570 cm.$^{-1}$ in dibenzyl disulphide, a reduction which would appear to be attributable at least in part to a diminution of the force constant involved. Thus, the C–S bond is apparently weakened even in the ground state of the

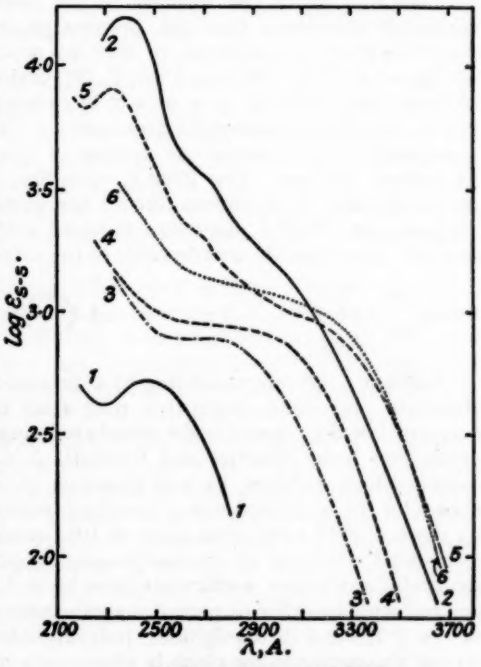
molecule, and hyperconjugation, formally expressed by excited structures like (VII*a* or *b*), may be recognised.

In contrast with dibenzyl disulphide itself, the very intense ultraviolet spectrum of its polynuclear derivative bis-(1 : 2-benz-10-anthrylmethyl) disulphide (VIII) has been reported to resemble that of the parent hydrocarbon 1 : 2-benzanthracene (Jones, *J. Amer. Chem. Soc.*, 1941, **63**, 151). The apparent absence of C–S bond hyperconjugation effects in this spectrum is presumably due to the relatively much greater stability of electronic levels derived from resonance within the highly conjugated aromatic nucleus.

Sulphur Monochloride.—Reference to the absorption spectrum and structure of this disulphide is pertinent to the succeeding discussion. Lorenz and Samuel (*Z. physikal. Chem.*, 1931, *B*, **14**, 219) inferred from the similarity of their published spectra of thionyl chloride ($SOCl_2$) and sulphur monochloride (S_2Cl_2) that the latter compound must resemble the former with respect to its branched type of structure. In the present work, however, the absorption of thionyl chloride was found to be markedly different from that reported by Lorenz and Samuel, and from the sulphur monochloride spectrum. The three new absorption curves recorded in Fig. 2 are clearly differentiated from one another, and furthermore in good accord with the vapour-absorption data subsequently published by Asundi and Samuel (*Proc. Physical Soc.*, 1936, **48**, 28). Although the possible existence of the branched type of sulphur monochloride structure as a transient and reactive unstable isomeric species cannot be altogether excluded (cf. Spong, *J.*, 1934, 485), electron-diffraction data (Ackermann and Mayer, *J. Chem. Physics*, 1936, **4**, 377; Palmer, *loc. cit.*), Raman spectra (Morino and Mizushima, *Sci. Papers Inst. Phys. Chem. Res.*, 1937, **32**, 220) and dipole-moment measurements (Scheibe and Stoll, *Ber.*, 1938, **71**, 1571) all point to the straight-chain disulphide formulation and moreover seem to support the static non-planar right-angled structure. Again, the observed ultraviolet absorption step-out in the region of 3000 A. ($\log \varepsilon = 3{\cdot}0$; curve 1, Fig. 2) will be recognised below as a characteristic feature of the electronically activated straight-chain disulphide linkage. As regards the more intense absorption maximum occurring at 2630 A., this must in some way be related to the resonance properties of the S–Cl bonds in the molecule.

FIG. 3.

Disulphides and polysulphides.



$$\varepsilon_{S-S} = \frac{\text{Molar extinction coefficient}}{\text{Number of S–S bonds in molecule}}$$

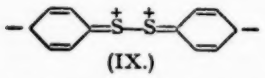
1. *Dicyclohexyl disulphide* (*in* EtOH).
2. *Diphenyl disulphide* (*in* EtOH).
3. *Sulphur* (*in* $CHCl_3$).
4. *Diethyl tetrasulphide* (*in* EtOH).
5. *Diphenyl tetrasulphide* (*in* EtOH).
6. *Dicyclohexyl hexasulphide* (*in* $CHCl_3$).

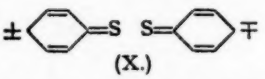
Diphenyl Disulphide.—*X*-Ray crystallographic analysis of the *pp'*-dibromo-derivative of diphenyl disulphide (Toussaint, *Bull. Soc. chim. Belg.*, 1945, **54**, 319) revealed a non-planar arrangement of substituents (azimuthal angle, 103°) about an unusually long S–S bond (2·15 A.) in the molecule; the C–S bond distances were apparently normal but probably not determined with a significant degree of accuracy in the crystal structure. The most characteristic chemical property of diphenyl disulphide is the reversible symmetrical dissociation into coloured free radicals, which takes place on heating in solvents (Schönberg, Rupp, and Gumlich, *Ber.*, 1933, **66**, 1932). The thermochromatic behaviour of solutions of both diphenyl disulphide and its *pp'*-dibromo-derivative was confirmed in the present work, the ready occurrence of free-radical dissociation being apparent even from the yellow colour of the pure melt in equilibrium with colourless solid diphenyl disulphide at 61°. The ultraviolet absorption spectrum of undissociated diphenyl disulphide (curve 2, Fig. 3; cf. also Chaix, *Bull. Soc. chim.*, 1933, **53**, 700) is characterised by a very intense maximum ($\log \varepsilon = 4{\cdot}2$) at 2380 A., preceded by two

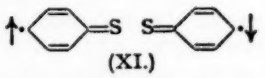
distinct inflections near 2700 and 3000 A. *pp'*-Dichloro- and *pp'*-dibromo-diphenyl disulphides give the same type of absorption curve, although displaced towards greater wave-lengths and intensities (maxima at 2420 A., log $\varepsilon = 4{\cdot}3$, and at 2480 A., log $\varepsilon = 4{\cdot}4$, respectively).

By analogy with the polar excited structures postulated for the related phenyl alkyl monosulphides (this vol., p. 392), *o*- and *p*-quinonoid resonance forms such as (IX) might be invoked to account for the intense absorption maximum of diphenyl disulphide, but this view is open to serious objections. Canonical structures containing like formal charges on adjacent atoms are regarded as intrinsically improbable (cf. Pauling, " The Nature of the Chemical Bond ", p. 184), and the structure (IX) moreover requires the benzene planes to be coplanar with the S–S bond, whereas in fact they are inclined at 36° to the latter in the crystal structure examined by Toussaint (*loc. cit.*).

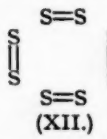
If, on the other hand, the previously recognised polarisation (II) is involved in the light absorption, it follows at once that in diphenyl disulphide the opposite formal charges on the two sulphur atoms can migrate to the benzene rings with which they are conjugated, and stabilised structures like (X) become plausible in the upper state. This kind of excited structure may be expected to lead to neutral radical dissociation of the central bond (cf. Mulliken, *J. Chem. Physics*, 1939, **7**, 20), and similar structures such as (XI) participating in the ground state probably play a part in causing the extra length of the disulphide bond quoted above, and its facile thermal dissociation. It seems likely, then, that the 2380 A. absorption is associated with a continuous system of quasi-conjugation of the benzene rings through the disulphide linkage. The 2700 A. shoulder, resembling the corresponding region of phenyl monosulphides, is doubtless due to the partial benzenoid chromophore (see Part I), and the step-out near 3000 A. may be compared with the corresponding shoulder in the spectrum of sulphur monochloride, attributable to the activated disulphide bond (see below).


(IX.)


(X.)


(XI.)

Sulphur.—Before proceeding to a discussion of polysulphides, it is of interest to consider the structure and light absorption properties of the stable sulphur molecule which exists as a symmetrical puckered eight-membered ring, S_8, both in the orthorhombic or the monoclinic crystalline form (Warren and Burwell, *J. Chem. Physics*, 1935, **3**, 6) and in the vapour at ordinary temperatures (Lu and Donohue, *J. Amer. Chem. Soc.*, 1944, **67**, 818). The preference shown for the octagonal size of the ring is presumably related to the fact that this is characterised by the favoured azimuthal angle of 103° occurring around each of the constituent bonds. The ultraviolet spectrum of crystalline sulphur in solution is plotted in Fig. 3. In this graph, all molecular extinction coefficients have been divided by the number of sulphur–sulphur linkages per molecule in order to permit a significant comparison between the absorption characteristics of the S–S bond in disulphides, polysulphides, and sulphur itself. Curve 3 shows that quite strong absorption takes place in elementary sulphur, intermediate between that of a saturated dialkyl disulphide (curve 1) and the conjugated diphenyl disulphide (curve 2). Some kind of mesomerism evidently occurs in the sulphur molecule. A formal extension of the resonance concepts applied in the formulations (II) and (X) or (XI) would lead to the hypothesis of two equivalent excited " Kekulé " forms of alternating no-bonds and double bonds (XII) participating in the structure, in addition to the conventional single-bond and various intermediate polar or formal-bonded excited canonical forms. The existence of appreciable resonance energy in the sulphur molecule has previously been inferred from thermal data by Powell and Eyring (*ibid.*, 1943, **65**, 648), but they suggested that each bond acquired some degree of double-bond character through donation of lone-pair non-bonding electrons to unfilled 3*d* orbitals. The observed normal single-bond distances of 2·1 A. (Warren and Burwell; Lu and Donohue; *locc. cit.*) and the non-planar configuration of the molecule would appear to favour no-bond–double-bond resonance rather than Powell and Eyring's multiple-bond formulation.


(XII.)

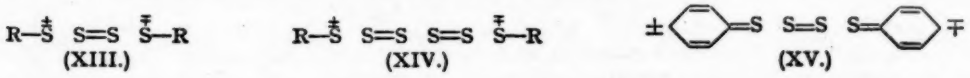
In plastic or elastic sulphur, the eight-membered rings are found to have broken down to give rise to long chains of sulphur atoms (Powell and Eyring, *loc. cit.*; Meyer and Go, *Helv. Chim. Acta*, 1934, **17**, 1081).

Polysulphides.—When allowance is made for additional bands due to the presence of phenyl groups, it emerges from Figs. 2 and 3 that the sulphur–sulphur bonds of sulphur monochloride, diphenyl disulphide, sulphur, diethyl tetrasulphide, diphenyl tetrasulphide, and di*cyclo*hexyl

hexasulphide all display characteristic absorption of the same spectral type, resembling the dialkyl disulphide spectrum displaced towards greater wave-lengths and intensities. In view of the known " linear " structure of dialkyl disulphides, sulphur monochloride, diphenyl disulphide, and sulphur, the close correspondence of all these curves may be taken as very strong evidence that the tetrasulphide and hexasulphide molecules are likewise composed of straight chains of sulphur atoms. No additional spectral features which might be ascribed to the presence of co-ordinated sulphur are discernible.

Some authors still seem to favour polysulphide formulations containing side-chain sulphur co-ordinately attached to a main di- or tri-sulphide chain, but with the possible exception of the *X*-ray data on thiokol (see below), all the more reliable evidence appears to be in support of the conclusion reached from ultraviolet spectra. The Raman frequencies of tri- and tetra-sulphides are reported to resemble those observed in elementary sulphur, none of which occur in the region to be expected for a co-ordinate sulphur–sulphur double bond (Hibben, " The Raman Effect and its Chemical Applications ", Reinhold, 1939, p. 259). Recent electron-diffraction results have established the linear character of the dimethyl trisulphide molecule (Donohue and Schomaker, *J. Chem. Physics*, 1948, **16**, 92). Similarly, unpublished *X*-ray data obtained by Mr. S. C. Nyburg (cf. also Dawson, Mathieson, and Robertson, *J.*, 1948, 322) indicate that the straight-chain but apparently not the hypothetical side-chain form of the *pp'*-dichloro-derivative of diphenyl tetrasulphide can be fitted into the observed unit-cell dimensions of the crystalline structure. By way of chemical evidence, spectrographically identical samples of diethyl tetrasulphide could be independently synthesised either from sodium tetrasulphide and ethyl bromide, or from sulphur monochloride and ethylthiol, a result which it is difficult to interpret on any but the straight-chain hypothesis of tetrasulphide structure (cf. Bloomfield, *J.*, 1947, 1547).

The observed shifts between the various sulphur–sulphur bond spectra recorded in Fig. 3 can be qualitatively accounted for by simple extension of the concept of S–S bond polarisation (II). The enhanced absorption of the saturated dialkyl tetrasulphide (curve 4) over the disulphide (curve 1) may be correlated with the fact that, in addition to the polar forms (II), further plausible conjugated polar structures (XIII) with a central double bond and two adjacent no-bonds would be expected to stabilise the excited level of the tetrasulphide. There may well be some connection between this type of excited structure and the observed chemical properties of diethyl tetrasulphide, in which two sulphur atoms can be removed rather easily to furnish the disulphide under a variety of conditions. Again, the still greater light absorption of a dialkyl hexasulphide (curve 6) follows from the possibility of yet further more highly conjugated polar structures (XIV) participating in the excited state. It should, perhaps, be pointed out that the great similarity of the *eight*-atom sulphur molecule absorption to that of the dialkyl *tetra*sulphide does not conflict with the proposed explanation of the observed chain-length effects, since special factors are known to come into play in cyclic resonators.



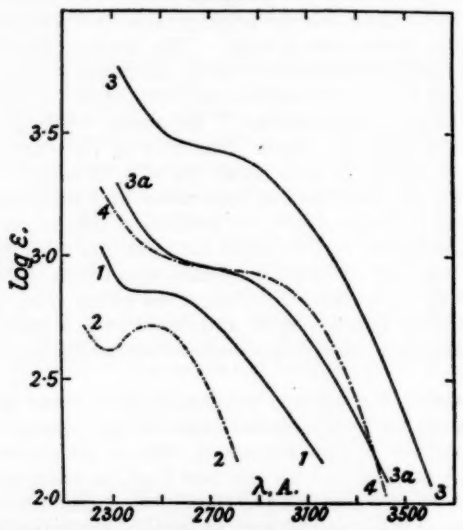
(XIII.) (XIV.) (XV.)

Replacement of alkyl by phenyl substituents in disulphides results in a very marked red shift and intensification of the first absorption region characteristic of the disulphide linkage (curves 1 and 2, Fig. 3). The origin of this strong activation may be sought in conjugation arising from contributions of the structures (X), which have already been postulated above in order to account for the high-intensity region of the diphenyl disulphide spectrum. A further long-wave displacement of the S–S bond absorption occurs in diphenyl tetrasulphide (curve 5), which resembles the disulphide at shorter wave-lengths, except that greater extinction values are shown in this region by the tetrasulphide when it is compared on the absolute molecular scale. Additional conjugation and contributions from the polar form (XV) in the excited state are plausible in correspondence with the related formulations above. Some significance may be attached to the fact that at 100°, when the saturated di*cyclo*hexyl tetrasulphide is quite stable, diphenyl tetrasulphide displays a tendency to decompose, giving rise to disulphide together with free sulphur or higher polysulphides (Bloomfield, *loc. cit.*).

Thiokols.—A typical disulphide thiokol of the polymeric ethylene–formal structure $([CH_2]_2{\cdot}O{\cdot}CH_2{\cdot}O{\cdot}[CH_2]_2{\cdot}S_2)_n$ furnished a spectrum akin to that of a simple dialkyl disulphide, as illustrated by curves 1 and 2 of Fig. 4. Similarly, polyethylene-tetrasulphide, $[(CH_2)_2S_4]_n$, was found to be virtually indistinguishable from monomeric diethyl tetrasulphide with respect to its ultraviolet-absorption properties (curves 3*a* and 4).

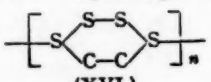
This result appears surprising in view of the common assumption that the latter thiokol contains two sulphur atoms co-ordinated to a disulphide chain in the repeat-unit structure, thereby differing from the straight-chain nature of diethyl tetrasulphide which is implicit in all the evidence outlined above. Although chemical arguments adduced in support of the co-ordinated structure of the polymeric tetrasulphide are not altogether convincing (cf. Bloomfield, *loc. cit.*), it has been stated on the basis of *X*-ray fibre diagrams (Fuller, *Chem.*

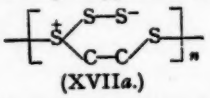
FIG. 4.
Thiokols.

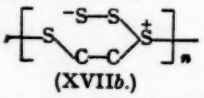


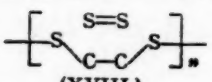
1. *Polyethyleneformal disulphide* (*in dioxan*).
2. *Dicyclohexyl disulphide* (*in* EtOH).
3. *Polyethylene tetrasulphide* (*in ethylene dichloride*).
3*a*. *do.* ε *values per* S–S *linkage.*
4. *Diethyl tetrasulphide* (*in* EtOH; ε *values per* S–S *linkage*).

Reviews, 1940, **26**, 160; cf. Katz, *Trans. Faraday Soc.*, 1936, **32**, 77) that the length of the polymer repeating unit (4·32 A.) is much too short to accommodate an unbranched tetrasulphide chain. Fuller (*loc. cit.*) advanced a cyclic structure (XVI) as the most plausible model, without, however, putting forward any suggestions as to the nature of the chemical bonds involved.


(XVI.)


(XVII*a*.)


(XVII*b*.)


(XVIII.)

Presumably, (XVII*a* and *b*) and (XVIII) would be contributing structures, and the considerable sulphur-bond resonance involved in the hybridisation might conceivably result in the observed ultraviolet-absorption properties resembling those of a linear diethyl tetrasulphide. It should be noted, however, that the *X*-ray diagrams given by tetrasulphide thiokol were apparently not altogether satisfactory, and that the proposed structural interpretation raises other difficulties of a more general nature. The cyclic co-ordination hypothesis does not link up well with recent views on the straight-chain character of elastic sulphur (see above), nor is it applicable to the repeat-units of polymeric diethylene ether tetrasulphide, $([CH_2]_2{\cdot}O{\cdot}[CH_2]_2{\cdot}S_4)_n$, or trimethylene tetrasulphide, $([CH_2]_3{\cdot}S_4)_n$, because of their different intramolecular spatial conditions, although the general properties of the latter thiokols are not reported to be different in any important respect. Considerable restrictions on free rotation of bonds, difficult to reconcile with rubbery properties, would also be imposed by the cyclic structure. It seems that further substantiation of Fuller's work must be awaited before the evidence against the linear tetrasulphide formulation of thiokol can be accepted without reserve.

EXPERIMENTAL.

Fig. 1.—Di*iso*amyl, di*cyclo*hexyl, and diallyl disulphides were prepared by Dr. F. W. Shipley in these laboratories. Two samples of di-*tert.*-butyl disulphide were synthesised by independent methods by

Dr. R. F. Naylor, the two preparations being identical in ultraviolet-absorption properties. A commercial sample of dibenzyl disulphide, after recrystallisation from ethanol, had m. p. 69—70°.

Fig. 2.—The sulphur–chlorine compounds were redistilled immediately before spectrographic examination, the monochloride over free sulphur at reduced pressure. Duplicate determinations were carried out in each case as a check against loss by volatilisation or hydrolysis, concordant results being obtained. All three chlorides obeyed Beer's law in dilute *n*-hexane solution.

Fig. 3.—Diphenyl disulphide was prepared by atmospheric oxidation of commercial thiophenol and crystallised in white matted needles, m. p. 60—61°, from ethanol. An abrupt colour change takes place at the m. p., the melt being yellow but re-solidifying to a pure white solid on freezing. Both diphenyl and *pp'*-dibromodiphenyl disulphides gave yellow solutions in hot solvents, which decolorised on cooling. The *pp'*-dibromo- and -dichloro-derivatives were obtained by courtesy of Drs. J. Toussaint and G. F. Bloomfield, respectively. The sulphur was a commercial crystallised sample, and the polysulphides described were obtained and purified by fractional or molecular distillation by Dr. G. F. Bloomfield in these laboratories. Diethyl tetrasulphide samples prepared from *either* sodium tetrasulphide and ethyl bromide *or* sulphur monochloride and ethylthiol gave identical ultraviolet absorption and other physical properties.

Fig. 4.—The two thiokols were kindly made available by Mr. M. Gordon of the Special Products Division, Dunlop Rubber Co., Ltd. The tetrasulphide thiokol was not attacked by cold organic solvents but gradually dissolved in hot ethylene dichloride or carbon disulphide from which solvents it could be recovered apparently unchanged as a yellow rubbery solid on evaporation. Two independently prepared solutions in ethylene dichloride gave completely identical absorption curves.

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[*Received, May 18th*, 1948.]

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92. *Absorption Spectra and Structure of Organic Sulphur Compounds. Part III. Vulcanisation Accelerators and Related Compounds.*

By H. P. KOCH.

Ultraviolet-absorption curves have been obtained for tetramethylthiourea, methyl dimethyldithiocarbamate, tetramethylthiuram mono- and di-sulphides, methyl, sodium, and zinc diethyldithiocarbamates, 2-mercaptobenzthiazole and its sodium and zinc derivatives, benzthiazolyl *N'-cyclo*hexyl 2-sulphenamide, and dibenzthiazolyl 2-di- and -tetra-sulphides. The resonance properties of these molecules are discussed.

Both tetramethylthiuram disulphide and dibenzthiazolyl 2-disulphide in solution give rise to thermochromasy, attributable to reversible thermal dissociation into coloured free radicals. Cyclic intramolecular interaction of non-bonded groups is suggested to account for some peculiar spectrographic and chemical properties of tetramethylthiuram disulphide. The absorption curves and structures of 2-mercaptobenzthiazole and its various derivatives can be divided into two distinct constitutional types arising from thioketo–thioenol mesomerism of the ion or radical of the parent compound. Varying degrees of co-ordination complex formation are apparent from the spectra of zinc diethyldithiocarbamate and bis-2-mercaptobenzthiazolezinc.

ULTRAVIOLET-ABSORPTION spectroscopy probably constitutes one of the most powerful methods of identification and analysis in the study of rubber vulcanisation accelerators and their transformation products, but little work has been published in this field (cf. Jarrijon, *Rev. Gén. du Caoutchouc*, 1943, **20**, 155). The majority of accelerator mixes in modern use contain various derivatives of the conjugated benzthiazolyl or dialkyldithiocarbamyl groups, both of which give rise to characteristic high-intensity absorption in the ultraviolet. The spectra of some typical members of these two classes have now been measured and recorded, together with those of certain structurally related molecules which are of assistance in the interpretation of bands. The practical application of such measurements to problems of rubber vulcanisation has already been referred to elsewhere (Jarrijon, *loc. cit.*; Koch, *India Rubber J.*, 1946, **61**, 145), and the following more fundamental account represents an attempt at correlation between ultraviolet absorption and the molecular structure and reactivity of sulphur-containing accelerators.

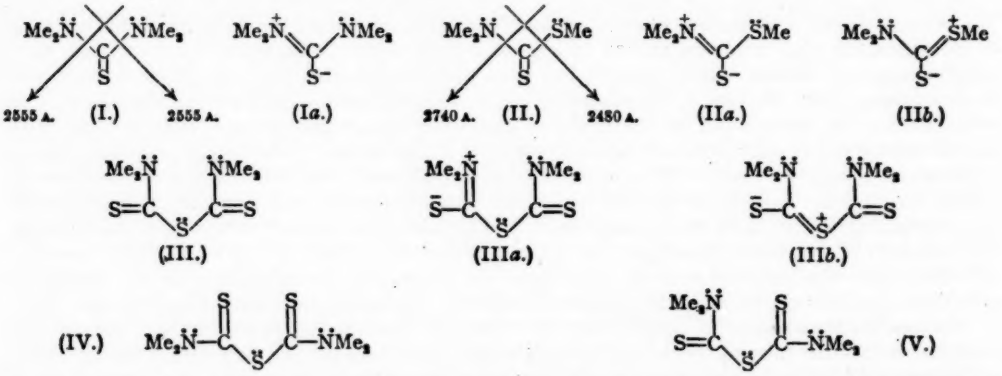
Tetramethylthiourea.—The absorption spectrum of tetramethylthiourea (I), one of the products of thermal decomposition of the accelerator TMT (see below), provides a valuable clue to the effect of conjugation between a thiocarbonyl group and a lone pair of electrons on an adjacent nitrogen atom. Intense absorption is displayed at 2555 A. ($\varepsilon = 17{,}000$; curve 1, Fig. 1), presumably associated with the presence of the polar structures (I*a*) in the excited state. Owing to the symmetry of the crossed-conjugated molecule, electric vectors oriented in two perpendicular directions in the plane of the chromophore (I) should be active in the absorption.

Methyl Dimethyldithiocarbamate.—In the carbamic ester molecule (II), the thiocarbonyl group is placed in crossed conjugation with a nitrogen and a sulphur atom, and two different polar excited structures (II*a* and *b*) may now be written corresponding to the two equivalent

forms (I*a*) above. In resemblance with the chromophoric behaviour of other unsymmetrical crossed-conjugated systems (*e.g.*, benzoyl sulphides, see Part I), two separate absorption regions may be recognised in the ultraviolet spectrum of methyl dimethyldithiocarbamate (curve 2, Fig. 1). The 2480 A. maximum ($\varepsilon = 8500$) is evidently due to conjugation with nitrogen (II*a*), being only slightly shifted from, and about half as intense as, the 2555 A. peak of tetramethylthiourea; and the new absorption at 2740 A. ($\varepsilon = 11{,}000$) must involve the sulphur conjugation (II*b*). Since the latter band occurs at lower frequencies than the former, it may be inferred that the excited structure (II*b*) lies nearer to the ground state than does (II*a*). This conclusion is in harmony with Pauling's electronegativity scale (" The Nature of the Chemical Bond ", p. 60), according to which the sulphur atom is more positive than nitrogen. The two characteristic electronic transitions have electric moments approximately at right angles to each other, and the respective light vectors active in the absorption may be visualised in two perpendicular directions in the plane of the molecule as shown in (II).

Tetramethylthiuram Monosulphide.—The bright yellow compound (III), known as " Thionex " or MS, displays a strong and rather broad absorption band at 2770 A. ($\varepsilon = 17{,}500$) whose tail reaches into the visible. On careful inspection of the recorded curve, a distinct inflection was also revealed in the neighbourhood of 2500 A. (curve 3, Fig. 1). By reference to the light-absorption properties of the two related molecules (I) and (II), it would seem that the intense maximum is due to sulphur conjugation (two equivalent polar excited structures, III*b*), and the partly masked short-wave band associated with the crossed conjugation of the dimethylamino-groups (III*a*). These excited levels require a coplanar configuration of the two NC=S groups, with an energy barrier opposing rotation about the central sulphide bonds. Three distinct stereoisomeric forms, (III), (IV), and (V), might then occur (cf. *cis*- and *trans*-butadiene), but only one stable modification of tetramethylthiuram monosulphide is actually known.

Tetramethylthiuram Disulphide.—The ultraviolet-absorption spectrum of the technically important " direct " vulcanisation accelerator generally known as TMT or " Tuads " (VI) is recorded as curve 4 in Fig. 1. In contrast with tetramethylthiuram monosulphide (III), the disulphide is almost colourless, but its solutions turn yellow on heating, reverting to colourless in the cold (thermochromasy). An absorption band is indicated near 2850 A. ($\varepsilon \sim 10{,}000$), but this merges into a second very intense short-wave region without any intervening minimum, the curve passing through an inflection near 2700 A. By comparison with the reported spectra of the monosulphide and of the related methyl dimethyldithiocarbamate, the relatively low intensity and ill-defined character of the long-wave absorption, and the greatly increased extinction at shorter wave-lengths appear anomalous in the spectrum of tetramethylthiuram disulphide. Reference to the chromophoric behaviour of diphenyl disulphide (this vol., p. 397) and of dibenzthiazolyl disulphide (see below) would suggest that the absorption of TMT should



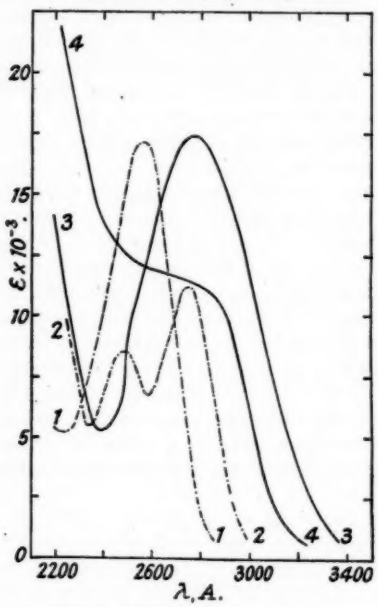
not be substantially different from twice the absorption of the " half "-chromophore represented by the ester molecule (II), but this expectation is not borne out by the curves 2 and 4 of Fig. 1. It seems as if some peculiar resonance process distinguishes the structure of TMT from that of other conjugated disulphides.

The chemical properties of tetramethylthiuram disulphide likewise exhibit some rather unexpected features which cannot be explained in terms of normal disulphide reactivity alone. For instance, in the presence of cyanide ion in solution, one of the sulphur atoms forming part

of the disulphide linkage is smoothly eliminated with the production of monosulphide (von Braun and Stechele, *Ber.*, 1903, **36**, 2275); and when heated to its melting point, tetramethylthiuram disulphide dissociates irreversibly and in good yield into tetramethylthiourea, carbon disulphide, and elementary sulphur (cf. Bloomfield, *J. Polymer Sci.*, 1946, **1**, 316). No explanation of these reactions has as yet been proposed.

FIG. 1.

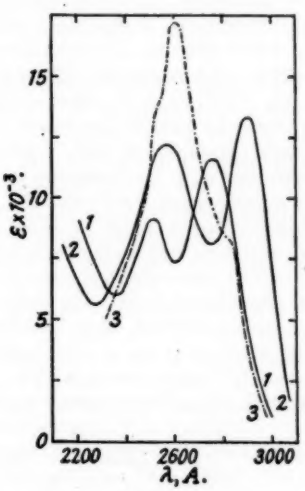
Dimethyldithiocarbamyl compounds.



1. *Tetramethylthiourea.*
2. *Methyl dimethyldithiocarbamate.*
3. *Tetramethylthiuram monosulphide.*
4. *Tetramethylthiuram disulphide.*

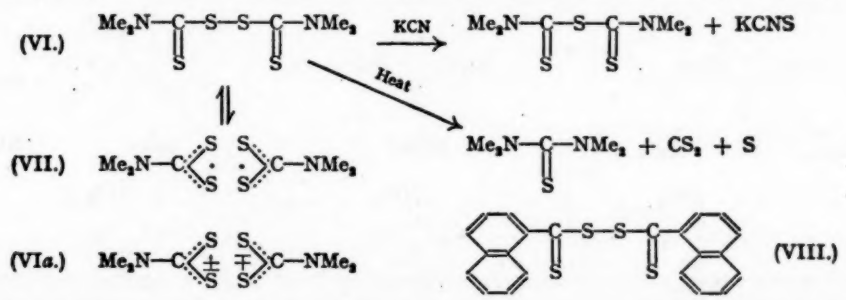
FIG. 2.

Diethyldithiocarbamic acid derivatives (*in* EtOH).



1. *Methyl ester.*
2. *Sodium salt trihydrate.*
3. *Zinc salt* (ε *per* Zn/2).

In view of the conventional mode of preparation by oxidative linking of two dimethyldithiocarbamic acid molecules, there can be little doubt about the normal straight-chain nature of the disulphide linkage in TMT. This assumption is in agreement with the above-mentioned thermochromatic properties, which accord with the corresponding behaviour of straight-chain diphenyl and dibenzthiazolyl disulphides, being attributable to reversible thermal dissociation of the disulphide link into coloured free radicals. Radical dissociation of the disulphide structure (VI) should be expected to occur very readily owing to extensive resonance stabilisation of the resulting dithiocarbamyl (VII). Similar dissociation takes place in the related molecules of dibenzoyl peroxide and di-α-dithionaphthoyl disulphide (VIII) (Schönberg *et al.*, *Ber.*, 1933,

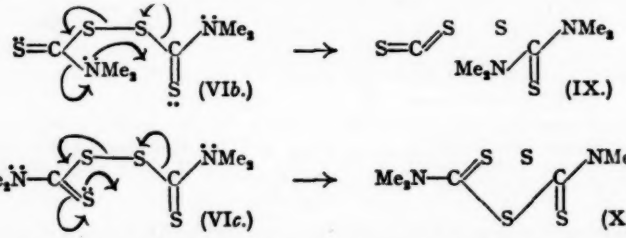


66, 1932). As a corollary of such facile bond fission, polar structures like (VI*a*) may be expected to be significant in the excited levels responsible for the observed spectrum of TMT. None of

these considerations offers any clue, however, to the peculiar spectroscopic and chemical characteristics which have been described above.

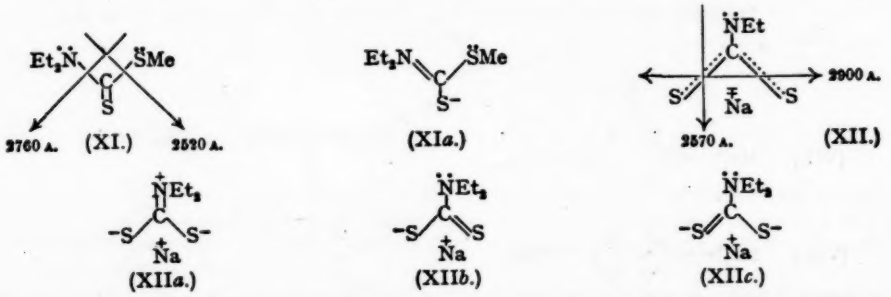
Additional electronic stabilisation may result from the special steric relationships in the thiuram disulphide structure, depicted by the two-dimensional diagrams (VI*b*) and (VI*c*). Such interaction would involve the intramolecular donation of a lone pair of electrons from one dimethylaminothiocarbonyl group towards the other, facilitated both by spatial proximity and by the possibility of further electron shifts completing the cyclic conjugation process indicated by the curved arrows. In view of the symmetry properties of the system, either half of the molecule could donate a bond to the other. It may, perhaps, be pointed out that the peculiar electron donation across space which is formulated in (VI*b*) merely represents the first step of the well-known addition of amino-groups to carbonyl or thiocarbonyl compounds, while the analogous interaction of double-bonded sulphur (VI*c*) should involve no special difficulty in view of the more strongly electropositive nature of sulphur as compared with nitrogen.

The cyclic intramolecular interaction hypothesis does not explain the rather featureless spectrum of TMT, but it does at least provide qualitative justification for the observed departure from the expected normal type. Moreover, the new postulate suggests a simple and rational overall mechanism for the peculiar chemical reactions of this compound. When carried to their extreme limit, the incipient electron shifts depicted by the curved arrows in (VI*b* and *c*) lead to the fragmentary structures (IX) and (X) respectively; and it has already been noted that at high temperatures TMT does in fact break down to (IX) (tetramethylthiourea, carbon disulphide, and free sulphur), while the presence of cyanide ion even in the cold promotes the formation of (X) (tetramethylthiuram monosulphide, and sulphur as thiocyanate). Although the detailed mechanism and the number of successive steps involved in these transformations have not been elucidated, they seem to suggest that the quasi-bonds donated across space as proposed in (VI*b* and *c*) are of real significance in the reactivity of TMT. The relative importance of the alternative conformations (VI*b* and *c*) of a given molecule may be a complex function of the comparative donor properties of nitrogen and sulphur and of the relative probabilities of



attaining the requisite geometrical conditions for intramolecular bond formation in the two cases.

Diethyldithiocarbamic Acid Derivatives.—In correspondence with the slightly more basic character of the diethyl- as compared with the dimethyl-amino-group (cf. Lewis, *J. Amer. Chem. Soc.*, 1945, **67**, 771), it was found that the absorption of methyl *N*-diethyldithiocarbamate (XI) occurred at slightly lower frequencies than that of the dimethyl compound (II) (cf. Figs. 1 and 2). The nitrogen conjugation band was displaced by 600 cm.$^{-1}$ from 2480 A. ($\varepsilon = 8500$) to 2520 A. ($\varepsilon = 9000$), whereas the sulphur conjugation maximum suffered a smaller shift of



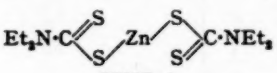
300 cm.$^{-1}$ from 2740 A. ($\varepsilon = 11{,}000$) to 2760 A. ($\varepsilon = 11{,}500$). The relative magnitude of these two shifts suggests that both excited (XI*a*) and ground (XI) states of the molecule are affected

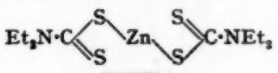
by the substitution. It may be assumed that other *N*-diethyl-substituted compounds of this class will behave in a similar manner and display absorption spectra only slightly different from those of the corresponding *N*-dimethyl derivatives. The general structural arguments advanced in this and the preceding sections are therefore regarded as relevant to dialkyldithiocarbamyl compounds generally.

Sodium diethyldithiocarbamate or SDC (XII) gives rise to the same general type of double-banded spectrum as the dialkyldithiocarbamic esters (ε = 13,000 at 2900 A., and ε = 12,000 at 2570 A.; cf. Fig. 2). The ground state doubtless approximates to the resonance hybrid (XII) and the two characteristic absorption regions can be vectorially assigned in perpendicular directions as shown. Absorption at 2570 A. results in polarisation of the nitrogen conjugation as before, the extreme structure (XII*a*) now being important in the excited state; and the 2900 A. maximum must be associated with the perpendicular oscillation of charge between the two sulphur atoms (extreme polar forms XII*b* and *c*).

Whereas the water-soluble sodium derivative (XII) obviously represents a true ionic salt, the corresponding zinc compound ZDC, insoluble in water but soluble in organic solvents, appears to involve covalent complex formation. The ultraviolet spectrum differs characteristically from that of the sodium salt (cf. Fig. 2). The 2900 A. absorption region attributed to charge-resonance in the ionic state no longer occurs, but a new and very intense narrow band at 2605 A. (ε = 17,000) is now superimposed on two shoulders near 2540 and 2820 A. which apparently correspond to the two absorption peaks of the methyl ester. These features seem compatible with the hybrid formulation (XIII) of the ground state, symmetrically

(XIII.)

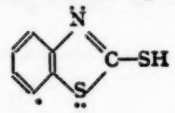

(XIII*a*.)


(XIII*b*.)

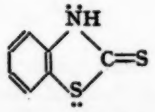
composed of two equivalent ester-analogous covalent-bond structures (XIII*a* and *b*) in resonance. The proposed constitution does not violate the known stereochemistry of either sulphur or zinc, and it probably finds an analogy in the structure of cupric dipropyldithiocarbamate, which has been shown to contain a molecular centre of symmetry (Peyronel, *Gazzetta*, 1943, **73**, 89). The valency configurations of copper and zinc being planar and tetrahedral respectively, no molecular symmetry centre would be expected to arise in the postulated zinc complex (XIII).

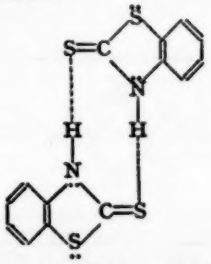
2-*Mercaptobenzthiazole and Metallic Derivatives.*—The vulcanisation accelerator MBT may in theory possess either of the alternative tautomeric structures (XIV) or (XV), but Morton and Stubbs have already shown that only (XV) exists in alcoholic solution, by comparing the observed spectrum with those of the sharply differentiated two stable methyl derivatives (*J.*, 1939, 1321). The absorption curve of MBT in ethanol was redetermined in the present work, in good agreement with that reported by Morton and Stubbs (curve 1, Fig. 3; ε = 27,500 at 3250 A., and ε = 15,000 at 2360 A.). It was further observed that almost identical bands occurred in benzene or chloroform solutions, so that the greater stability of the thiocarbonyl (XV) over the thiol form (XIV) appears to be independent of the nature of the solvent. Hunter found that association takes place in concentrated solution, doubtless by way of hydrogen bonding (*J.*, 1945, 806); and since a preliminary *X*-ray investigation by Dr. G. A. Jeffrey (private communication) has revealed that pairs of molecules are geometrically related by a centre of symmetry in the crystalline structure, it seems probable that MBT exists in the form of the symmetrical bimolecular complex (XVI) in the solid state.

(XIV.)



(XV.)



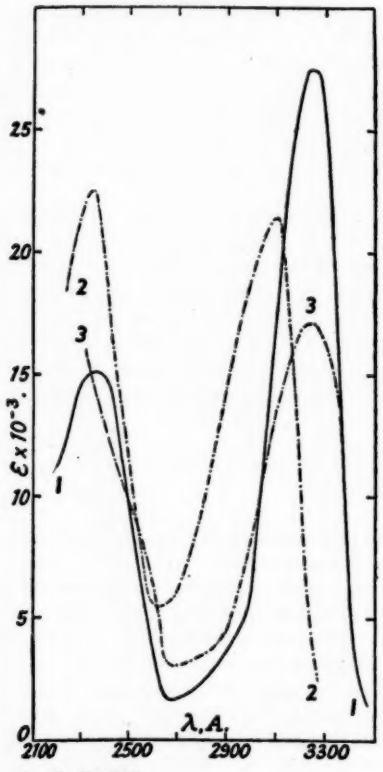

(XVI.)

No complete interpretation of the 2-mercaptobenzthiazole spectrum will be attempted here in view of the paucity of further reference data, but it would seem that (XV*a*, *b*, *c*, and *d*) represent the most obvious polar excited structures. Accordingly, it is suggested that the very intense long-wave absorption band which constitutes such a unique feature of MBT may be

correlated with the formal oscillation of negative charge between the two ends of the molecule. Deep colour is known to result from this type of charge-resonance involving a large transition

FIG. 3.

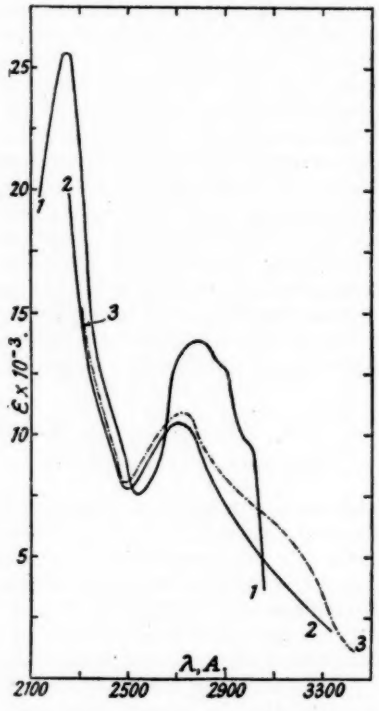
2-Mercaptobenzthiazole.



1. *In* EtOH.
2. *In* 2N *aq.* NaOH.
3. *Zinc salt* (*in* $CHCl_3$; ε *per* Zn/2).

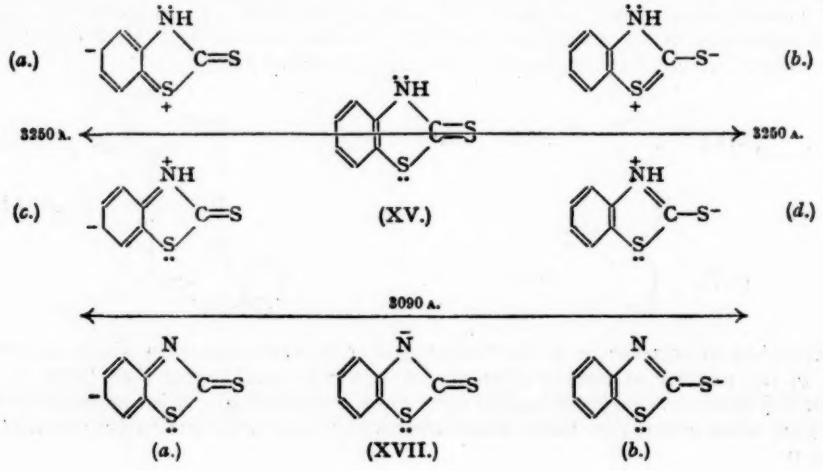
FIG. 4.

2-Benzthiazolyl compounds (*in* EtOH).



1. *2-Benzthiazolyl* N'-cyclo*hexyl sulphenamide.*
2. *Di-(2-benzthiazolyl) disulphide* (ε *per mol. wt.* × ½).
3. *Di-(2-benzthiazolyl) tetrasulphide* (ε *per mol. wt.* × ½).

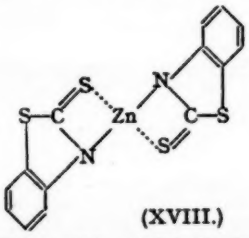
moment (Pauling, Gilman's " Organic Chemistry ", 2nd edtn., 1943, p. 1982). A similar band is observed in the anion (XVII) (curve 2; ε = 21,500 at 3090 A., and ε = 22,500 at 2340 A.),



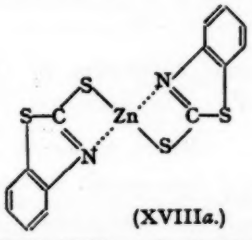
but not in the derivatives of the thiol form (XIV) (see below), in which charge-resonance is precluded.

The highly insoluble zinc derivative of MBT again exhibits the characteristic long-wave absorption ($\varepsilon = 17{,}000$ at 3240 A.; curve 3, Fig. 3), but the intensity is reduced and no second band is observed near 2350 A., although this arises in both MBT and its *N*-alkyl derivatives (Morton and Stubbs, *loc. cit.*). Some modification of the thiocarbonyl structure (XV) is therefore indicated, and it may be assumed that co-ordination complex formation occurs (XVIII). The primary valency attachment of the heavy metal is still formulated at the nitrogen atom in view of the previously identified charge-resonance band in the spectrum, but the alternative sulphur-linked structure (XVIII*a*) is thought to make some contribution. The resonance degeneracy of the metallic bonds would not be expected to be complete as it is in the dithiocarbamyl complex (XIII) on account of the non-equivalence of the two postulated extreme canonical structures (XVIII) and (XVIII*a*).

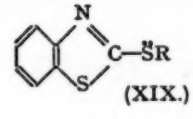
Organic Derivatives of 2-Mercaptobenzthiazole.—The spectrum of the sulphenamide known as HBS or " Santocure " (XIX; R = $NH{\cdot}C_6H_{11}$) closely resembles that of 2-methylthiobenzthiazole (XIX; R = Me) as recorded by Morton and Stubbs, so that the constitution of this compound as a derivative of the hypothetical thiol form (XIV) of MBT cannot be in doubt. Two maxima occur, one at 2245 A. ($\varepsilon = 25{,}000$), and the other at 2780 A. ($\varepsilon = 13{,}500$), with subsidiary fine-structure bands superimposed on the near-ultraviolet slope (curve 1, Fig. 4). The 2780 A. absorption region can probably be assigned to the system of conjugation depicted by the classical and polar excited forms (XIX) and (XIX*a*) respectively.



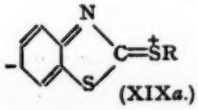
(XVIII.)



(XVIII*a*.)



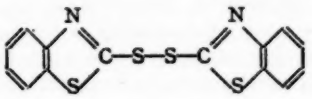
(XIX.)

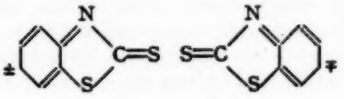


(XIX*a*.)

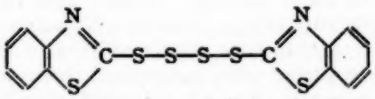
Dibenzthiazolyl 2-disulphide or MBTS (XX) again displays absorption of the same general type as that of the thiol-derived structures (XIX) (curve 2, of Fig. 4; $\varepsilon/2 = 10{,}500$ at 2710 A.). The typical long-wave tail characteristic of conjugated S–S bonds can also be recognised (this vol., p. 397), and the importance of the polar structures (XX*a*) in the excited state inferred by analogy with the case of diphenyl disulphide which has been discussed in the preceding paper. A predisposition for facile reversible dissociation into neutral free radicals may again be predicted and is evidently responsible for the observed thermochromatic properties of MBTS solutions.

(XX.)





(XX*a*.)



(XXI.)

Finally, the constitutional type of the reaction product of MBT with sulphur monochloride was confirmed as the tetrasulphide (XXI) by comparison of its spectrum (curve 3, Fig. 4; $\varepsilon/2 = 10{,}900$ at 2730 A.) with that of the disulphide (XX). The " bulge " in the curve near 3000 A. may be identified with the enhanced absorption of linear tetrasulphides in that spectral region (this vol., p. 397).

Experimental.

Fig. 1.—Tetramethylthiuram mono- and di-sulphides were commercial recrystallised samples. The monosulphide was bright yellow, and the practically colourless disulphide was thermochromatic in benzene or ethanol solutions but did not turn yellow on heating in the solid state until it decomposed irreversibly at its m. p. (146°). The compound obeyed Beer's law in dilute alcoholic solution at room temperature. Tetramethylthiourea (m. p. 78°) was prepared by Dr. F. W. Shipley, and methyl dimethyldithiocarbamate (white needles, m. p. 46°) obtained in these laboratories by Mr. A. L. Morris from carbon disulphide, dimethylamine, and methyl iodide (cf. Delépine, *Bull. Soc. chim.*, 1902, **27**, 591).

Fig. 2.—Sodium and zinc diethyldithiocarbamates were purified from commercial samples by

recrystallisation. The sodium salt was obtained as the trihydrate in thin irregular plates, m. p. 92—102°, from acetone (Found: C, 26·9; H, 7·45; S, 28·55; Na, 10·2. Calc. for $C_5H_{10}NS_2Na,3H_2O$: C, 26·7; H, 7·15; S, 28·45; Na, 10·2%), and the zinc salt in large transparent crystals, m. p. 177°, from benzene. *X*-Ray examination of the latter compound, kindly carried out by Mr. S. C. Nyburg, revealed the presence of four molecules in a monoclinic unit cell ($a = 9·96$, $b = 10·62$, $c = 15·45$ A.; $\beta = 105°$) with the space-group symmetry $P2_1/n$. The dilute alcoholic solutions were found to obey Beer's law. (No quartz-ultraviolet absorption was displayed by alcoholic solutions of zinc chloride.)

Methyl diethyldithiocarbamate (b. p. 120°/16 mm.) was prepared by reaction of the corresponding sodium salt with methyl iodide in alcoholic solution.

Fig. 3.—A commercial sample of 2-mercaptobenzthiazole gave large, ochre-yellow, monoclinic needles (cell dimensions: $a = 15·2$, $b = 6·01$, $c = 8·04$ A.; $\beta = 100°$), m. p. 178°, on recrystallisation from benzene. The observed space-group symmetry $P2_1/n$, with four molecules in the unit cell, requires that pairs of molecules are related by a centre of symmetry in the crystal structure (*X*-ray data by courtesy of Dr. G. A. Jeffrey). Light absorption in benzene: $\lambda_{max.} = 3290$ A., $\varepsilon = 25{,}000$; in $CHCl_3$: $\lambda_{max.} = 3209$ A., $\varepsilon = 24{,}500$.

The zinc derivative of 2-mercaptobenzthiazole was prepared and purified by Dr. G. F. Bloomfield.

Fig. 4.—Dibenzthiazolyl 2-disulphide was obtained in irregular white leaflets on recrystallisation from benzene. The solid compound remained colourless when heated to its m. p. (179—180°), whereat a yellow melt was produced which re-set to a white solid on cooling. Thermochromasy was displayed by the solutions in benzene and alcohol. Dibenzthiazolyl 2-tetrasulphide was prepared by Dr. F. W. Shipley from 2-mercaptobenzthiazole and sulphur monochloride.

2-Benzthiazolyl *N'-cyclo*hexyl sulphenamide ("Santocure") was a commercial sample which furnished off-white (light ochre) needles, m. p. 102—103°, on crystallisation from aqueous ethanol (Found: S, 24·0. Calc. for $C_{13}H_{16}N_2S_3$: S, 24·3%).

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[*Received, May 18th*, 1948.]

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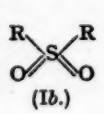
93. *Absorption Spectra and Structure of Organic Sulphur Compounds. Part IV. Unsaturated Sulphones.*

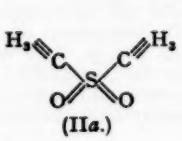
By H. P. KOCH.

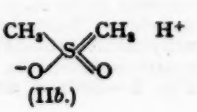
Existing physical and chemical data support the view that conjugation occurs with a sulphonyl group adjacent to double bonds, lone-pair electrons, or C–H bonds. This phenomenon affords a consistent interpretation of the recorded ultraviolet-absorption curves of phenyl alkyl, diphenyl, and *pp'*-dibromodiphenyl sulphones, but the evidence regarding the intramolecular geometrical conditions required by such conjugation appears ambiguous. Spectrographic measurements on dibenzyl sulphone and the α- and β-isoprene sulphones are also reported. The bond-length data of Cox and Jeffrey on β-isoprene sulphone are reinterpreted in terms of hyperconjugation.

THE nature of the valency bonds in sulphones has recently been in dispute (cf. Phillips, Hunter, and Sutton, *J.*, 1945, 146), mainly as a result of Lister and Sutton's unexpected discovery that the S–O bond distances are extremely short in dimethyl sulphone (*Trans. Faraday Soc.*, 1939, **35**, 495; cf. also Cox and Jeffrey, *ibid.*, 1942, **38**, 214; Palmer, *J. Amer. Chem. Soc.*, 1938, **60**, 2360). The measured bond-length value of 1·44 A. appeared incompatible with the generally accepted co-ordinate single-bond formulation (I*a*), which was based on Lewis's octet theory and seemingly supported by the observed approximately tetrahedral distribution of the four sulphur valencies (Lister and Sutton; Cox and Jeffrey; Palmer; *locc. cit.*; Toussaint, *Bull. Soc. chim. Belg.*, 1945, **54**, 319). According to Phillips, Hunter, and Sutton, the alternative double-bond formulation (I*b*) affords a more satisfactory representation of the constitution of sulphones. The latter view has now been reconciled with the modern theory of valency (Kimball, *J. Chem. Physics*, 1940, **8**, 188). The primary four σ-bonds undoubtedly arise from tetrahedral sp^3 hybridisation in the ($3s$, $3p^3$) shell of doubly ionised sulphur (cf. Gurjanova, *J. Physical Chem. Russia*, 1943, **17**, 65), but two $3d$ orbitals are said to be additionally available for the formation of two strong π-bonds (valency shell "expansion"), and weaker π-bonds can apparently also be formed with two further $3d$ orbitals. These ideas readily account for the tetrahedral sexacovalent valency state of sulphur in the sulphones. The observed shortening of the S–O bonds may be attributed to double-bond formation (I*b*) arising through donation of electron pairs from the negative oxygen atoms in the primary structure (I*a*) to the unfilled $3d$ orbitals of the positive sulphur atom.

(I*a*.)


(I*b*.)


(II*a*.)

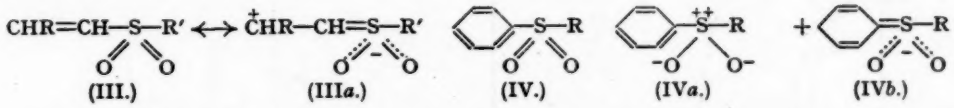

(II*b*.)

The following observations are chiefly concerned with conjugation phenomena occurring in unsaturated sulphones, and it will be shown that the electronic interaction between sulphonyl and organic functional groups can be consistently described in terms of the double-bonded ground-structure (I*b*). Nevertheless, the possible existence of minor resonance contributions from the single-bond form (I*a*) may be tacitly understood in every case.

It is to be noted that the sulphur–oxygen bonds in saturated dialkyl sulphones differ from the double bonds of carbonyl, carboxyl, nitro-, and nitroso-groups, all of which give rise to weak ultraviolet absorption, in being completely transparent to wave-lengths greater than 1800 A. (Ley and König, *Z. physikal. Chem.*, 1938, *B*, **41**, 365, and observations by the author on dimethyl sulphone). Evidently, no suitable excited levels exist in the sulphone grouping.

Hyperconjugation in Saturated Sulphones.—Rothstein (*J.*, 1937, 309) has shown that the marked activation of C–H bonds by adjacent sulphonyl groups cannot be accounted for purely in terms of the inductive effects associated with the formal positive charges in the structure (I*a*) (cf. Hochberg and Bonhoeffer, *Z. physikal. Chem.*, 1940, *A*, **184**, 419). Additional mesomeric effects were postulated, causing the C–H bond electrons to become partly donated to the neighbouring C–S linkage. Such hyperconjugation can be described in terms of alternative extreme canonical structures such as (II*a* and *b*).

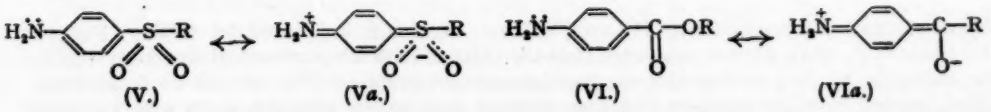
αβ-*Unsaturated Sulphones.*—" Expansion " of the sulphur valency octet has been invoked by a number of authors in order to explain the marked resemblance in chemical properties between αβ-unsaturated aliphatic sulphones and the analogous conjugated carbonyl compounds (cf. Kohler and Potter, *J. Amer. Chem. Soc.*, 1935, **57**, 1316). On the basis of the double-bonded ground-structure (I*b*), the resonance formulation (III and III*a*) provides a satisfactory description of the conjugation characteristics.



(III.) (III*a*.) (IV.) (IV*a*.) (IV*b*.)

Aromatic Sulphonyl Compounds.—The well-known *m*-directing properties of aromatic sulphonyl groups (IV) might be attributed to either inductive or mesomeric electron-attractive effects, arising respectively from the formal positive charge (IV*a*) or from $d\pi$-bond formation and conjugation (IV*b*). The special significance of mesomerism is, however, revealed in the marked bathochromic influence on the ultraviolet spectrum of benzene which is exerted by sulphonic substituents (Böhme and Wagner, *Ber.*, 1942, **75**, 606; Kumler and Strait, *J. Amer. Chem. Soc.*, 1943, **65**, 2349; Doub and Vandenbelt, *ibid.*, 1947, **69**, 2714): no corresponding effect is produced by substituted ammonium groups in anilinium cations which equally carry a positive pole but are incapable of double-bond mesomerism because of the non-availability of stable *d*-orbitals in the nitrogen atom.

The aromatic conjugation of sulphonyl groups becomes enhanced when a basic amino-group is placed in the *p*-position of the ring. Thus, Kumler and Halverstadt (*ibid.*, 1941, **63**, 2182) concluded from dipole-moment measurements that the polar excited form (V*a*; R = NH_2) of sulphanilamide makes up some 3% of the ground state of the molecule, comparable with the 2·5% provided by the analogous polar form (VI*a*; R = OMe) in the ground state of methyl *p*-aminobenzoate. The characteristic ultraviolet-absorption spectra of sulphanilamide and *p*-aminobenzoic acid likewise present a striking resemblance (Kumler and Strait, *loc. cit.*; Havinga and Veldstra, *Rec. Trav. chim.*, 1947, **66**, 257), and the obvious correspondence between these two molecules is of considerable interest in connection with their significant relationship in bacterial metabolism.

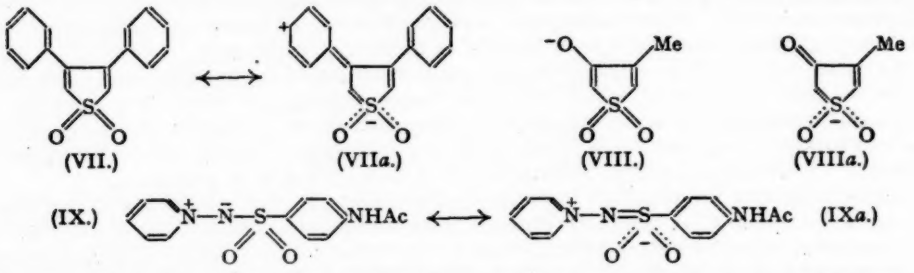


(V.) (V*a*.) (VI.) (VI*a*.)

In the dye field, sulphonic substitution in the aromatic nucleus *para* to the nitrogen atom of azo- or azoxy-derivatives similarly produces well-known auxochromic effects which may be attributed to charge-separated polar canonical resonance structures analogous to (V*a*) (cf. Fierz-David *et al.*, *Helv. Chim. Acta*, 1946, **29**, 1718).

Other indications of the conjugating power of the sulphonyl group in more complex aromatic systems may be obtained from the literature. Resonance hybridisation and low-energy polar

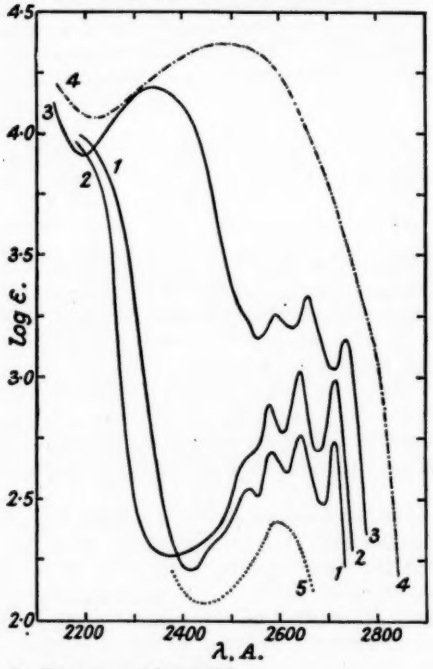
forms (VII*a*) are presumably associated with the marked stability and visible-light absorption of 3 : 4-diphenylthiophen sulphones (VII) (Hinsberg, *Ber.*, 1915, **48**, 1611); and the intense



yellow colour displayed by the anion of 4-hydroxy-3-methylthiophen sulphone (VIII) (Backer and Strating, *Rec. Trav. chim.*, 1935, **54**, 170) appears to find a plausible explanation in the

FIG. 1.

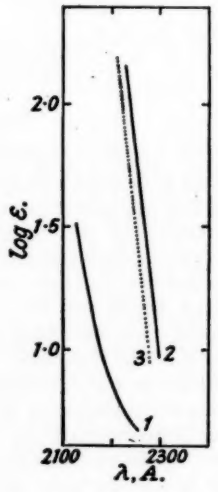
Phenyl sulphones (*in* EtOH).



1. *Benzenesulphonamide.*
2. cyclo*Hexyl phenyl sulphone.*
3. *Diphenyl sulphone.*
4. pp'-*Dibromodiphenyl sulphone.*
5. *Dibenzyl sulphone* (ε *per mol. wt.* × ½).

FIG. 2.

Isoprene sulphones (*in* EtOH).



1. β-*Isoprene sulphone.*
2. α-*Isoprene sulphone.*
3. *Methyl*cyclo*hexene* (*in* C_6H_{11}).

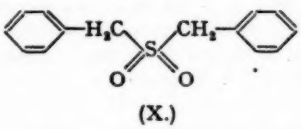
charge-resonance formulation (VIII and VIII*a*). Again, Bell (quoted by Ashley, Buchanan, and Easson, *J.*, 1947, 64) has suggested that the chief contributory canonical structure stabilising the molecule of *N*-(*p*-acetamidobenzenesulphonimido)pyridine (IX) should be formulated as (IX*a*), arising from conjugation of a lone electron pair on the nitrogen atom with the double-bonded sulphone group.

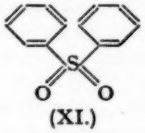
Absorption Spectra of cyclo*Hexyl Phenyl and Diphenyl Sulphones.*—Some new ultraviolet-absorption data presented in Fig. 1 may now be described against the background given above. No previous spectral measurements appear to have been made on phenyl alkyl sulphones, and only the fine-structure region of the spectrum of diphenyl sulphone was recorded by Chaix (*Bull. Soc. chim.*, 1933, **53**, 700). Fig. 1 includes a fresh determination of the benzenesulphon-

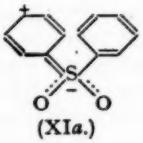
amide absorption for purposes of comparison (cf. Böhme and Wagner; Kumler and Strait; *locc. cit.*), as well as the spectra of *pp'*-dibromodiphenyl and dibenzyl sulphones.

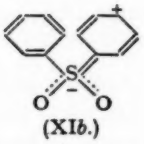
The marked conjugating effect of a sulphone group directly attached to the benzene ring is apparent from the relative aromatic absorptions of *cyclo*hexyl phenyl (IV; R = C_6H_{11}) and dibenzyl (X) sulphones (curves 2 and 5). The latter spectrum resembles the weak absorption of a simple alkylbenzene, but *cyclo*hexyl phenyl sulphone absorbs somewhat more strongly even than benzenesulphonamide (IV; R = NH_2), with fine-structure maxima at identical wave-lengths in the two conjugated sulphonyl compounds (2715, 2645, and 2580 A.; curves 2 and 1). The light-absorption properties of both 1- and 2-methyl*cyclo*hexyl phenyl sulphones were completely identical with those of the unsubstituted *cyclo*hexyl derivative.

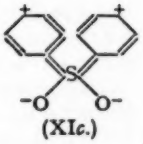
Further modification arises in the spectrum of diphenyl sulphone (XI; curve 3). The fine-structure region has now become displaced by 250 cm.$^{-1}$ to the red (max. at 2735, 2660, and 2595 A.), and intense absorption also occurs at 2350 A. (log $\varepsilon = 4{\cdot}2$). The new band may represent a shift of the 2150 A. region of the monophenyl sulphonyl compounds (cf. Doub and Vandenbelt, *loc. cit.*), or it may be due to a novel type of conjugation in the structure, similar to that invoked for diphenyl sulphide (this vol., p. 392). From the latter point of view, the two benzene rings would be quasi-conjugated *via* one of the 3*d* orbitals of the sulphur atom, and charge-resonance involving the two equivalent structures (XI*a* and *b*) would occur. This state of affairs seems unlikely, however, owing to the proven non-coplanarity of the two benzene rings in the molecular structure (see below). More probably, the possibility of additional polarisation, depicted by the extreme excited structure (XI*c*), plays a part in shifting the spectrum from that observed for the monophenyl sulphonyl compounds.


(X.)

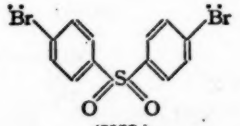

(XI.)

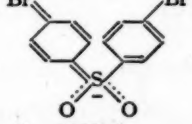

(XI*a*.)

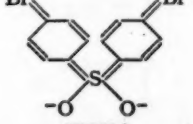

(XI*b*.)


(XI*c*.)

The spectrum of the *pp'*-dibromo-derivative (XII) is of particular interest in view of a recent *X*-ray analysis of its crystal structure and molecular geometry by Toussaint (*loc. cit.*). The characteristic high-intensity transition of diphenyl sulphone appears to be facilitated by *pp'*-dibromination, since an even stronger broad maximum is now observed around 2500 A. (log $\varepsilon = 4{\cdot}37$), while the fine-structure region has become entirely masked except for the " kink " reproduced in curve 4 of the figure. The bathochromic influence of the bromine substituent may be compared with the corresponding effect of *p*-amination on the spectrum of benzenesulphonamide (see above), being presumably associated with stabilisation of the positive charge in the polar excited forms (XI*a* and *b*) through donation of lone electron pairs from the halogen atoms [structures (XII*a* and *b*)]. It may be noted that the frequency shift resulting from *pp'*-bromination is about twice as large in diphenyl sulphone as it is in diphenyl sulphide (this vol., p. 392), mesomeric and inductive effects respectively being invoked in the two cases.


(XII.)

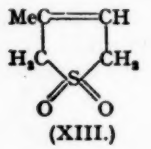

(XII*a*.)

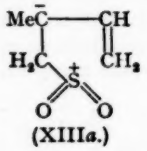

(XII*b*.)

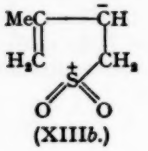
The proposed resonance contributions from (XII*a* and *b*) suggest that in *pp'*-dibromodiphenyl sulphone the S–C bonds should be short and the S–O bonds slightly lengthened relative to the corresponding bonds in the conventional formulation (XII). Toussaint (*loc. cit.*) derived apparently normal ($1{\cdot}84 \pm 0{\cdot}04$ A.) S–C but unusually long ($1{\cdot}54 \pm 0{\cdot}05$ A.) S–O bond distances from his *X*-ray measurements, comparison here being made with the electron-diffraction data on dimethyl sulphone as standard (Lister and Sutton, *loc. cit.*). The O–S–O bond angle of 131° also appears to be unexpectedly wide (cf. Jeffrey and Cox, *loc. cit.*). In view of the relatively large experimental errors inherent in the analytical method employed, the significance of these results may be doubtful, but if anything, they seem to support the postulated resonance. The observed geometrical configuration of the molecule is of more considerable interest. It is found that the two benzene rings as well as the plane of the sulphone group are arranged at

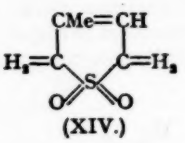
right angles to the plane formed by the two sulphur–carbon links. In the corresponding sulphide and similar conjugated systems (cf. Toussaint, *loc. cit.*; and Part I), the benzene rings are always as nearly *coplanar* as is compatible with the steric requirements of the structure, the resulting near-planar arrangement affording the maximum possible resonance stabilisation. Since the two benzene rings lie in *perpendicular* planes in the observed structure of *pp'*-dibromodiphenyl sulphone, it must be concluded that mutual resonance interaction cannot occur. On the other hand, a maximum of conjugation between each phenyl group separately and the sulphone grouping may well result from the perpendicular configuration observed in the crystal, although definite knowledge regarding the relevant symmetry properties of the postulated π-bonding 3*d* orbitals of sulphur seems to be lacking. It should be noted, however, that resonance interaction between sulphonyl and unsaturated bonds apparently also takes place in the necessarily *planar* cyclic systems of the thiophen and isoprene sulphones (VIII and XIII). The experimental evidence concerning the geometrical conditions of sulphone conjugation is evidently ambiguous. It may perhaps be significant in this connection that Kimball (*loc. cit.*) predicted the possibility of two different types of π*d*-bonds with sulphur on theoretical grounds.

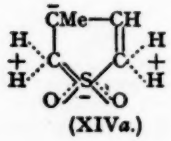
The Structure of β-*Isoprene Sulphone.*—Butadiene and many of its homologues combine with sulphur dioxide to form stable crystalline cyclic sulphones, the chemistry of which has been extensively studied by Backer, Zujdewijn, and others (cf. Suter, " The Organic Chemistry of Sulphur; Tetracovalent Sulphur Compounds ", Wiley, 1944, p. 729). Cox and Jeffrey (*loc. cit.*) carried out an accurate *X*-ray determination of the bond-parameters of β-isoprene sulphone (XIII), and they found that all the links forming part of the heterocyclic ring had hybrid character, being intermediate in length between single and double bonds. For instance, while " normal " bond-distances were observed for S–O (1·44 A.) and C–Me (1·54 A.), the three cyclic C–C bonds measured 1·41 A. and the C–S bonds 1·75 A. (all values ± 0·02 A.). In order to account for these unusual features, Cox and Jeffrey suggested resonance with the two virtually equivalent polar forms (XIII*a* and *b*), although no supporting evidence was adduced from the valency characteristics of other βγ-unsaturated sulphones. This formulation is not now regarded as a plausible interpretation of the experimental results. First, it does not account for the observed S–C bond-distances of 1·75 A. which are *very* short compared with the corresponding parameters in dimethyl sulphone (1·90 ± 0·03 A., according to Lister and Sutton, *loc. cit.*). Secondly, the proposed resonating structures (XIII) and (XIII*a* and *b*) involve divergent positions in space of the methylenic hydrogen atoms, if anything like the normal geometrical bond arrangement around saturated and unsaturated carbon atoms is to be preserved; moreover, the required planar trigonal distribution of the two hydrogens attached to the >C=C grouping in (XIII*a* and *b*) is precluded by the cyclic conformation of the structure. Thirdly, the described hypothesis entirely fails to account for the very pronounced α-methylenic reactivity of β-isoprene sulphone (C–H bonds unstable towards Grignard reagent, dilute alkali, or ultraviolet light).

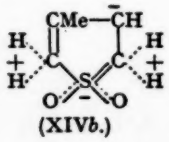

(XIII.)

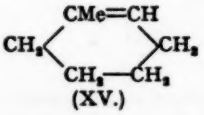

(XIII*a*.)

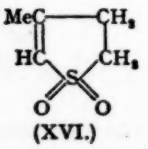

(XIII*b*.)


(XIV.)


(XIV*a*.)


(XIV*b*.)


(XV.)


(XVI.)

Cox and Jeffrey also suggested that hyperconjugation, the possibility of which is implicit in the formal structural representation (XIV), might be an additional cause of the abnormal cyclic bond lengths in β-isoprene sulphone. Since hyperconjugation phenomena must assume greatly enhanced significance when the C=H_2 bonds are adjacent to *two* unsaturated groupings and furthermore attached to a cyclic system (cf. *cyclo*pentadiene, Hannay and Smyth, *J. Amer. Chem. Soc.*, 1946, **68**, 244), no serious inconsistency arises from the absence of any measurable shortening in the exocyclic carbon–methyl bond. Clearly, the existence of extensive hyperconjugation in β-isoprene sulphone accounts both for the partial double-bond character of all the cyclic bonds, and also for the marked α-methylenic reactivity of the molecule as previously pointed out

by Rothstein (*loc. cit.*). Resonance between (XIV) and the two virtually equivalent forms (XIV*a* and *b*) is proposed, in place of the discarded set of resonating structures (XIII, XIII*a* and *b*). If all three forms (XIV, XIV*a* and *b*) are assumed to be equally important in the ground state, maximum resonance stabilisation would result and each of the bonds in the ring become endowed with 33% double-bond character, in conformity with the measured length (1·41 A.) of the three cyclic C–C bond distances. The strength of the methylenic C–H bonds would at the same time be reduced by 33% no-bond character. The S–O linkages should also become lengthened relatively to those found in dimethyl sulphone, but the latter effect could apparently not be observed experimentally.

β-Isoprene sulphone is highly transparent to ultraviolet light, absorbing considerably less than would be expected from the conventional formula (XIII). This phenomenon is illustrated in Fig. 2, where the absorption of the sulphone (curve 1) is compared with that of the tri-substituted cyclic ethylenic bond in methyl*cyclo*hexene (XV; curve 3). Low-energy excited absorbing states of the molecule evidently do not exist. On the other hand, the ultraviolet absorption of the αβ-unsaturated α-isoprene sulphone (XVI; curve 2) resembles that of the analogous simple double-bond compound (XV), with little spectrographic evidence of sulphonyl conjugation.

Experimental.

Dimethyl sulphone was prepared by the method of Lister and Sutton (*loc. cit.*) and recrystallised from water; m. p. 108°.

Fig. 1.—Commercial samples of benzenesulphonamide and of diphenyl sulphone were recrystallised from ethanol; m. p. 151—152° and 123—124° (cf. Mikeska, Farinacci, and Bogert, *J. Amer. Chem. Soc.*, 1936, **58**, 1869), respectively. Dibenzyl sulphone was prepared according to Shriner, Struck, and Jorison (*ibid.*, 1930, **52**, 2067) and obtained in needles, m. p. 149—150°, from ethanol. This substance was insoluble in 20% aqueous sodium hydroxide solution. *cyclo*Hexyl and 1- and 2-methyl*cyclo*hexyl phenyl sulphones were pure crystalline samples prepared by Dr. J. I. Cunneen (*J.*, 1947, 36). A specimen of *pp'*-dibromodiphenyl sulphone was kindly supplied by Dr. J. Toussaint.

Fig. 2.—The isoprene sulphones were recrystallised from water, the starting material being that also employed by Cox and Jeffrey for *X*-ray analysis. β-Isoprene sulphone melted at 63—63·5°, and α-isoprene sulphone (needles) at 78—79°. The methyl*cyclo*hexene curve is taken from Bateman and Koch (*J.*, 1944, 600).

The author is greatly indebted to his colleagues for their help in making available the samples for spectrographic examination. Their individual contributions have been acknowledged in the Experimental parts of this and the preceding papers of the series, but particular thanks are due to Drs. G. F. Bloomfield, J. I. Cunneen, G. A. Jeffrey, S. C. Nyburg, and F. W. Shipley for much valuable additional information, and to Mr. M. Gordon of the Dunlop Rubber Co. for specimens of pure thiokol. It also gives much pleasure to thank Dr. J. Toussaint (University of Liége) for affording many opportunities of comparing the spectrographic investigation with his own *X*-ray studies in the same field. The present series of papers is based on work forming part of a programme of fundamental research on rubber undertaken by the Board of the British Rubber Producers' Research Association.

British Rubber Producers' Research Association,
48, Tewin Road, Welwyn Garden City, Herts. [*Received, May 18th*, 1948.]

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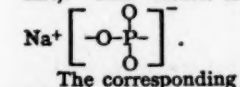
94. *The Condensed Phosphoric Acids and Their Salts. Part I. Metaphosphates.*

By C. W. Davies and C. B. Monk.

The preparations reported in the literature for various sodium metaphosphates have been repeated, and the conductivity of the products has been examined. Evidence is found only for the trimetaphosphate, the tetrametaphosphate, and a colloidal *n*-metaphosphate (Graham's salt). This result is reasonable if the monomeric unit is regarded as the unstable



The corresponding acids have been obtained from the salts by means of cation-exchange resins. *n*-Metaphosphoric acid is colloidal, and unstable in water; the other two are relatively stable, and very strong acids—the third dissociation constant of the trimeta-acid being comparable with the second dissociation constant of sulphuric acid.

The interaction of the three forms with the calcium ion has been studied by a solubility method.

Condensed phosphate systems have been the subject of much study, and the voluminous literature has recently been reviewed by Yost and Russell (" Systematic Inorganic Chemistry ",

Prentice-Hall, 1944) and Quimby (*Chem. Reviews*, 1947, **40**, 141). Much of the earlier confusion was resolved by the thermal and *X*-ray studies of Partridge, Hicks, and Smith (*J. Amer. Chem. Soc.*, 1941, **63**, 454) and of Boullé (*Compt. rend.*, 1935, **200**, 658), which have clearly differentiated between a number of solid sodium phosphates. These are tabulated by Quimby, though other metastable forms may yet, of course, be added to the list.

Evidence regarding aqueous solutions, and the ionic species existing in them, is much less satisfactory. Two methods, in the main, have been used: the calculation of molecular weights from freezing-point depressions, and the application of "Ostwald's rule" to approximate conductivity measurements. These have been applied to the sodium salts, with the primary object of determining the valency of the anion. The first method is not entirely convincing, because even in those cases where activity corrections have been applied, there is considerable room for uncertainty as to the extent of complex formation and ion-association in these multivalent electrolytes. Conclusions drawn from Ostwald's rule are equally hazardous. The rule states that the equivalent conductivity of a salt at 25° is less at a dilution of $v = 32$ than at $v = 1024$ litres by $10n$, where n is the valency product of the ions. The rule holds fairly well for a great many salts, but it fails for the orthophosphates, and has never been adequately tested for ions of valency greater than two. In practice, it has been used to support the accepted formulæ of some of the condensed phosphoric acids, but has been disregarded where it does not agree with evidence from other sources.

Our object was to identify more exactly the anions present in aqueous solutions of the various condensed phosphates reported in the literature. First, conductivity measurements were carried out with highly dilute solutions of the sodium salt. These revealed any abnormality in dissociation, furnished evidence, by comparison with Onsager's equation, of the valency of the anion, and further characterised the latter by its mobility. The stability of the salt towards water could also be estimated from the extent, if any, to which the conductivities showed a drift with time. Next, the conductivity of the corresponding acid was measured, and dissociation constants calculated; this further characterised the anion, and also showed to what extent the sodium salt solutions were affected by hydrolysis. Finally, since interest in the condensed phosphates is largely concerned with their power of sequestering calcium in dilute solutions, the extent of complex formation between the anion and calcium ion was determined by a solubility method.

Trimetaphosphates.—Sodium trimetaphosphate. Several investigators have prepared a soluble, crystalline metaphosphate for which Yost and Russell accept the formula $Na_3P_3O_9$, on the evidence of freezing-point determinations by Nylèn (*Z. anorg. Chem.*, 1936, **229**, 30). Quimby assigns the same formula to the salt, but apparently with some reserve.

We followed Jones's method of preparation (*Ind. Eng. Chem. Anal.*, 1942, **14**, 536), and confirmed his finding that the salt thus obtained is free from ortho-, pyro-, and "hexameta-" phosphate. The densities of aqueous solutions of the salt were measured and found to be represented, up to $C = 0{\cdot}01$, by the equation $d_4^{25°} = 0{\cdot}99707 + 0{\cdot}0695C$, where C is the equivalent concentration. The conductivities at 25°, for two separate preparations, are tabulated below. Col. 1 gives the number of the preparation, col. 2 the specific conductivity of

Conductivity of sodium trimetaphosphate solutions at 25°.

Batch.	$10^6\kappa_{H_2O}$.	10^3C.	$10^4C\sqrt{}$.	Λ.	α.	K_3.	Batch.	$10^6\kappa_{H_2O}$.	10^3C.	$10^4C\sqrt{}$.	Λ.
1	0·425	117·67	108·5	130·52	0·9985	0·070	2	0·25	1484·8	385·3	122·14
2	0·453	243·21	156·0	129·08	0·9970	0·069			2724·4	522·0	118·66
		348·24	186·6	128·13	0·9957	0·067			8172·1	904·0	109·76
		472·90	217·5	127·15	0·9940	0·063	1	0·26	1805·5	424·9	121·28
1	0·44	879·76	296·6	124·74	0·9913	0·071			3902·0	624·7	116·01
		1406·1	375·0	122·46	—	—			6784·6	823·7	111·04
		2478·2	497·8	119·25	—	—			14255	1194	104·19
		3944·5	628·0	115·94	—	—					
		6529·0	808·0	111·83	—	—					

the solvent water, col. 3 the equivalent concentration, col. 4 its square root, and col. 5 the equivalent conductivity of the salt. The normal solvent correction has been applied, allowance being made for interionic-force effects (Davies, *Trans. Faraday Soc.*, 1929, **25**, 129). The salt is relatively stable in water, for the conductivities of the dilute solutions did not alter perceptibly (that is, to the extent of 1 part in 20,000) over periods of an hour.

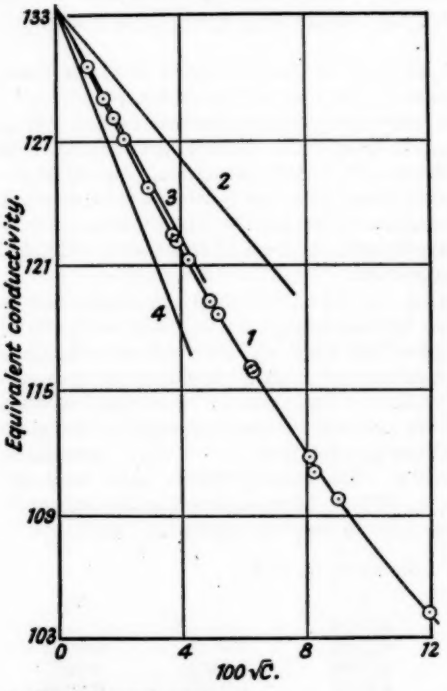
The results are shown in Fig. 1, plotted against the square root of the concentration. A linear extrapolation from the most dilute points gives $\Lambda_0 = 133{\cdot}70$, and after deduction of 50·11 for the mobility of the sodium ion (Shedlovsky, *J. Amer. Chem. Soc.*, 1932, **54**, 1411), the mobility

of the metaphosphate ion becomes 83·59. Fig. 1 also shows the theoretical limiting slopes, calculated from Onsager's equation, for the possible salts $Na_2P_2O_6$, $Na_3P_3O_9$, and $Na_4P_4O_{12}$. The very close agreement of experiment with the second of these clearly provides strong evidence that the anion is tervalent. There is a small deviation in the concentration range around 0·001N, the experimental points falling slightly below the theoretical line; but this type of deviation is precisely what has been found for other 1-3-valent electrolytes such as potassium ferricyanide and hexamminocobaltic chloride (Hartley and Donaldson, *Trans. Faraday Soc.*, 1937, **33**, 465) and potassium cobalticyanide (James, Ph.D. Thesis, London, 1947), and is explained by the slight degree of ion association to be expected with electrolytes of this valency type.

Only an approximate calculation of the extent of ion association is possible. At the lowest concentrations we can assume that two sodiums per molecule are completely dissociated, and

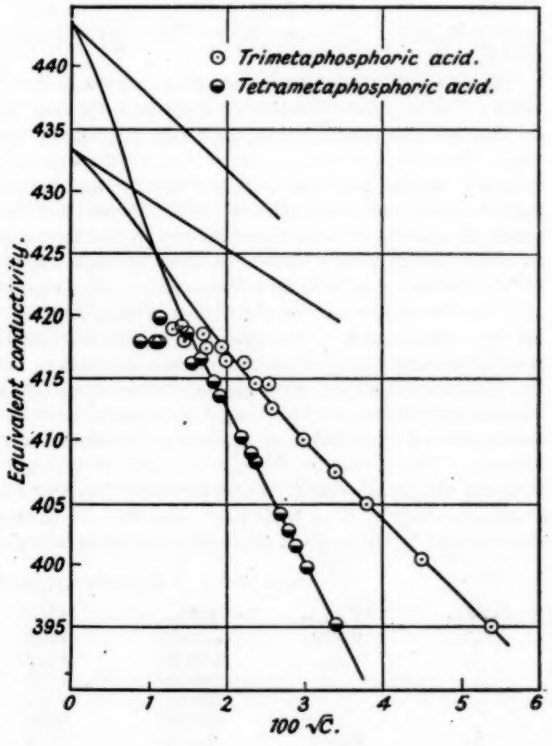
FIG. 1.

Equivalent conductivity of sodium trimetaphosphate at 25°.



1, *Experimental curve.*
2, 3, 4, *Onsager limiting slopes for* 1-2-*valent,* 1-3-*valent and* 1-4-*valent salt, respectively.*

FIG. 2.



write α for the degree of dissociation of the ion NaP_3O_9''. At a molar concentration m, therefore, we can regard the salt as a mixture of the 1-3-valent electrolyte $3Na^{\cdot}P_3O_9'''$, of concentration αm, and the 1-2-valent electrolyte $2Na^{\cdot}NaP_3O_9''$, of concentration $(1 - \alpha)m$. For the purpose of calculating interionic-force corrections we assume that both salts show the same conductivity in the mixture as they would in pure solutions of the same total ionic strength. We must also assume a value for the mobility of the NaP_3O_9'' ion, and for this two-thirds of 83·59, *i.e.*, 55·73, has been taken. Onsager's equation may now be used to calculate conductivities for the two forms, and for the molecular conductivity of the salt we obtain :

$$3\Lambda_{expt.} = 3\alpha(133{\cdot}70 - 201{\cdot}5\,I^{\frac{1}{2}}) + 2(1 - \alpha)(105{\cdot}84 - 135{\cdot}3\,I^{\frac{1}{2}})$$

where I, the ionic strength, is given by $I = \frac{1}{2}[12\alpha m + 6(1 - \alpha)m] = (1 + \alpha)C$. These equations are solved by successive approximations, and the values of α obtained are shown in

col. 6 of the above table. The values of the dissociation constant, given in col. 7 of the table, are calculated from the relation

$$K = \frac{\{Na^{\cdot}\}\{P_3O_9'''\}}{\{NaP_3O_9''\}} = \frac{f_1f_3(2+\alpha)\alpha m}{f_2(1-\alpha)}$$

where the ion-activity coefficients, f_1, f_2, f_3 are found from the Debye–Hückel limiting equation $\log f_i = -0{\cdot}509z_i^2I^{\frac{1}{2}}$, z_i being the valency of the ion.

The mean value of the dissociation constant is $K = 0{\cdot}068$. The chief uncertainties in the calculation are: (*a*) the value of the intermediate ion's mobility, (*b*) the extent of departure from the limiting Onsager equation at the concentrations studied. If the value 60 is taken in place of 55·73 for the intermediate ion's mobility, the dissociation constant is unchanged, and the constancy is the same as before. The error due to the second cause is more difficult to assess, but the absence below 0·001N of a trend in the K values implies that it is small. The value $K = 0{\cdot}068$ corresponds on Bjerrum's electrostatic theory of ion association to a closest distance of approach of the sodium and trimetaphosphate ions of 8·41 A.

Trimetaphosphoric acid. A stock solution of the acid was prepared by passing a solution of the sodium salt through a column of the cation-exchange resin Amberlite I.R.-100 in the hydrogen form. The conversion into acid was complete to within 0·2%, the limit of sensitivity of the analysis.

The conductivity results are given in the following table in the same form as in the previous table. No solvent correction was deducted when calculating the equivalent conductivity.

Trimetaphosphoric acid does not appear to have been prepared or studied before. It is relatively stable in water, the conductivities showing no change over considerable periods. It is a very strong acid, as is shown by the high conductivities, but the comparison (Fig. 2) of the experimental conductivities with the theoretical Onsager slope indicates that dissociation is not quite complete; the Λ_0 value shown in the figure was obtained by adding 349·82, the mobility of the hydrogen ion (MacInnes, Shedlovsky, and Longsworth, *J. Amer. Chem. Soc.*, 1932, **54**, 2758), to the value found for the anion in the preceding section.

The dissociation constant of the HP_3O_9'' ion has been calculated in exactly the same way as for the sodium salt. The mobility of the intermediate ion has again been assumed to be 55·7; a small error in this value is even less important with the acid than with the sodium salt, since the main result of the association process is the disappearance of a highly mobile hydrogen ion. The measurements at the lowest concentrations have had to be neglected; as is usual when a strong acid is measured in a glass cell, these points are affected by ion-exchange at the glass surface. The K values also show a drift at concentrations greater than $C = 0{\cdot}001$, presumably through the break-down of the limiting Onsager equation. The most probable value over the available range is $K = 0{\cdot}009$, but this may be in error by 20%. This implies that the extent of (immediate) hydrolysis of trimetaphosphates when dissolved in water is negligibly small.

Conductivity of trimetaphosphoric acid solutions at 25°.

Batch.	$10^6\kappa_{H_2O}$.	10^6C.	$10^5C\frac{1}{2}$.	Λ.	α.	K_3.
1	0·389	208·67	1445	419·10	—	—
		298·26	1727	418·56	0·9556	0·0053
		389·34	1973	417·40	0·9551	0·0067
		506·52	2251	416·16	0·9550	0·0086
		652·87	2555	414·60	0·9536	0·0103
2	0·219	103·50	1142	417·80	—	—
		172·79	1315	418·91	—	—
		219·08	1480	417·91	—	—
		310·32	1762	417·44	—	—
		402·20	2006	416·35	0·9494	0·0061
		570·11	2388	414·57	0·9486	0·0082
3	0·551	670·81	2590	412·52	0·9411	0·0082
		901·30	3002	410·03	0·9365	0·0099
		1158·2	3403	407·62	0·9321	0·0111
3	0·551	1452·4	3811	405·03	—	—
		2052·8	4531	400·39	—	—
		2905·3	5390	394·96	—	—

Interaction of trimetaphosphate ion with calcium ion. The solubility of calcium iodate in sodium trimetaphosphate solutions at 25° is given in the first two columns of the following table; the first shows the molar concentration of the trimetaphosphate solution, and the second the solubility of calcium iodate, in moles per litre, in this solution. The increase in solubility is considerably greater than occurs in sodium or potassium chloride solutions of the same ionic

strength, and the simplest explanation of this, which is borne out by the quantitative treatment, is that extensive association occurs between the multivalent ions to give CaP_3O_9'; further interaction between this and other (*e.g.*, calcium) ions is negligible at the concentrations considered.

The quantitative treatment of the results has been carried out in the way described by Wise and Davies (*J.*, 1938, 273). Allowance has to be made for the species $CaIO_3^+$, $NaIO_3$, and NaP_3O_9'', and the bases of the calculation are the known dissociation constants of these ($CaIO_3^+$, $K = 0{\cdot}13$; $NaIO_3$, $K = 3{\cdot}0$), the solubility product of calcium iodate, $S_0 = 7{\cdot}141 \times 10^{-7}$, and Davies's ion-activity coefficient equation (*J.*, 1938, 2093). The results are given in cols. 3—10 of the table, concentrations being in millimols. per litre; the correct values are reached by successive approximations, that of CaP_3O_9' being obtained by difference. Col. 11 gives the ionic strength of the solution, and col. 12 the dissociation constant of CaP_3O_9', calculated from

Solubility of calcium iodate in sodium trimetaphosphate solutions at 25°.

$Na_3P_3O_9$.	$Ca(IO_3)_2$.	$NaIO_3$.	NaP_3O_9''.	$CaIO_3^+$.	IO_3'.	Na^+.	Ca^{++}.	CaP_3O_9'.	P_3O_9'''.	I.	$K.10^4$
0	0·00785	—	—	—	—	—	—	—	—	—	—
0·003353	0·00906	0·04	0·06	0·44	17·64	9·96	6·29	2·33	0·96	0·03221	3·45
0·006677	0·01016	0·09	0·23	0·41	19·81	19·73	5·71	4·04	2·42	0·04477	3·47
0·01332	0·01187	0·19	0·91	0·39	23·16	38·86	5·24	6·24	6·17	0·07439	3·34
0·02005	0·01317	0·30	1·91	0·36	25·68	57·94	5·13	7·68	10·46	0·1070	3·12

the relation $K = f_2f_3[Ca^{++}][P_3O_9'''']/f_1[CaP_3O_9']$. The values are very steady, the mean K being 0·00033. This is a constant of the same order of magnitude as those of the other 2—3-valent complexes so far studied (Davies, *J.*, 1930, 2421; 1945, 463). On Bjerrum's theory it corresponds to a mean ionic diameter of 4·15 A.

Tetrametaphosphates.—The first detailed study of tetrametaphosphates was due to Warschauer (*Z. anorg. Chem.*, 1903, **36**, 137), who based his evidence for a four-fold polymerisation on Ostwald's rule. Yost and Russell quote cryoscopic evidence which they regard as doubtful. The compounds are not mentioned by Quimby.

Sodium tetrametaphosphate. The sodium salt was prepared by Warschauer's method, *via* the copper salt, and purified by several crystallisations from conductivity water. The conductivity results are given below, and are plotted in Fig. 3, which also shows earlier measurements by Warschauer and Tammann. Extrapolation of our results gives a limiting conductivity of 143·80, so that the mobility of the anion is 93·69. The experimental slope is less than that required by Onsager's equation for a 1-5-valent electrolyte; it is somewhat greater than the theoretical slope for a 1-4-valent salt, but this is to be expected since ion-association is

Conductivity of sodium tetrametaphosphate solutions at 25°.

Batch.	$10^6\kappa_{H_2O}$.	10^4C.	$10^4C\Lambda$.	Λ.	α.	K.
1	0·387	244·00	1562	135·97	—	—
		419·40	2048	133·81	0·9665	0·0089
		578·83	2406	131·93	0·9574	0·0090
		779·67	2792	129·85	0·9462	0·0090
		1109·4	3339	127·09	0·934	0·0095
		1436·4	3790	124·85	0·922	0·0096
		2106·8	4590	121·09	(0·908)	(0·0104)
2	0·355	105·37	1027	137·18	—	—
		151·15	1230	136·66	—	—
		223·24	1494	135·65	—	—
		423·55	2058	133·54	0·9621	0·0079
		567·95	2383	131·98	0·9561	0·0086
		807·44	2842	129·69	0·9467	0·0093

considerable in salts with a valency product of four. The extent of ion association has been calculated in the way already described for trimetaphosphate, the effect at the low concentrations studied being attributed to the formation of the ion NaP_4O_{12}''', and the mobility of this being taken as $\frac{3}{4} \times 93{\cdot}69 = 70{\cdot}27$. The results are in the last two columns of the table, and the mean value of K, the dissociation constant of the ion NaP_4O_{12}''', is 0·009, corresponding on Bjerrum's theory to a mean ionic diameter of the sodium and tetrametaphosphate ions of 6·40 A. The only dissociation constant available for comparison is the value 0·005 found for potassium ferrocyanide (Davies, *J. Amer. Chem. Soc.*, 1937, **59**, 1760). The value of the dissociation constant, the anion's mobility, and the slope of the conductivity curve all support the quadrivalency assumed for the anion.

Tetrametaphosphoric acid. Stock solutions were prepared from the sodium salt by treatment with Amberlite I.R.-100. Resistance measurements showed no change with time, so this acid,

too, is relatively stable in dilute aqueous solution. The conductivities are tabulated below, and plotted in Fig. 2. The figure also shows the theoretical Onsager slope, and it will be seen

FIG. 3.

Conductivity of sodium tetrametaphosphate at 25°.

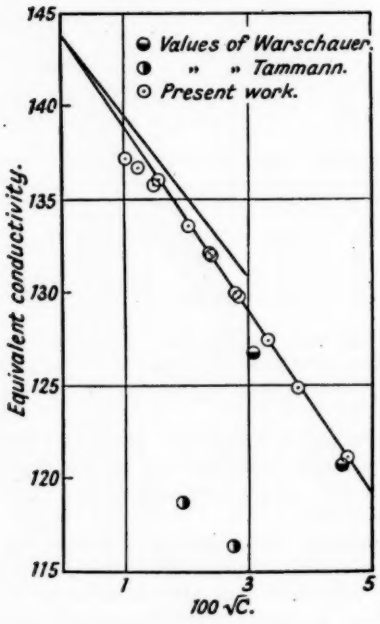
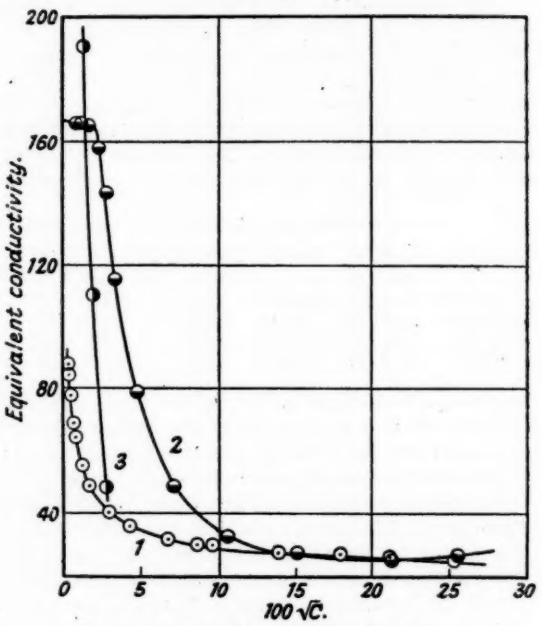


FIG. 4.



1, *Sodium " hexametaphosphate."*
2, *Octadecylamine hydrochloride.*
3, *" Hexametaphosphoric " acid.*

that dissociation of the acid is not complete. The dissociation constant for the last hydrogen has been calculated, as before, the equation used being

$$\Lambda = 315{\cdot}07 + \alpha(128{\cdot}44 - 14{\cdot}82I^{\frac{1}{2}}) - 226{\cdot}02I^{\frac{1}{2}},$$

where $I = (1{\cdot}5 + \alpha)C$. The values of α and K are shown in the table. The most dilute points had to be neglected, as in the case of trimetaphosphoric acid, but the others give a satisfactory constant with a mean value $K_4 = 0{\cdot}0018$.

Conductivity of tetrametaphosphoric acid solutions at 25°.

Batch.	$10^6\kappa_{H_2O}$.	10^3C.	$10^3C\sqrt{}$.	Λ.	α.	K_4.
1	0·379	82·00	907	417·25	—	—
		136·43	1168	419·81	—	—
		190·95	1381	418·95	—	—
		286·90	1694	416·45	—	—
		565·94	2379	408·23	0·8231	0·0018
		837·28	2894	401·38	0·7882	0·0019
2	0·331	232·04	1523	418·55	—	—
		345·87	1860	414·72	0·8536	0·0015
		549·87	2345	408·93	0·8282	0·0018
		794·95	2820	402·73	0·7963	0·0020
3	0·252	126·09	1123	417·81	—	—
		250·42	1583	416·06	—	—
		371·95	1929	413·46	0·8465	0·0015
		489·33	2215	410·26	0·8326	0·0017
		739·90	2720	403·97	0·8023	0·0019
		932·16	3053	399·69	0·7808	0·0020
		1162·2	3409	395·18	0·7579	0·0021

Interaction of tetrametaphosphate ion with calcium ion. The measurements and calculations were made in the same way as for the trimetaphosphate ion, except that here allowance must be made, even at low concentrations, for both stages in the association: $Ca^{\cdot\cdot} + P_4O_{12}^{\prime\prime\prime\prime} \rightleftharpoons CaP_4O_{12}^{\prime\prime}$; $Ca^{\cdot\cdot} + Ca_2P_4O_{12}^{\prime\prime} \rightleftharpoons Ca_2P_4O_{12}$. The two dissociation constants cannot be calculated independently from the measurements, and the less important—that for the first

dissociation of calcium tetrametaphosphate—was therefore given the preliminary value $K_1 = 0{\cdot}0037$, which is the value previously found (James, *loc. cit.*) for the comparable salt calcium ferrocyanide. Calculations on this basis gave K_2 values for the second-stage dissociation which altered markedly with concentration. We have therefore proceeded, by trial and error, to determine the two dissociation constants which simultaneously give the best fit for the experimental solubilities. They are: $K_1 = 0{\cdot}0022$ and $K_2 = 1{\cdot}3 \times 10^{-5}$, corresponding on the Bjerrum theory to 3·28 A. for the mean ionic diameter of calcium and tetrametaphosphate ions and 4·00 A. for that of the calcium and calcium–tetrametaphosphate ions. The results are in the following table.

Solubility of calcium iodate in sodium tetrametaphosphate solutions at 25° : $K_1 = 0{\cdot}0022$.

$Na_4P_4O_{12}$.	$Ca(IO_3)_2$.	$NaIO_3$.	NaP_4O_{12}'''.	$CaIO_3^+$.	IO_3'.	Na^+.	Ca^{++}.	CaP_4O_{12}''.	$Ca_2P_4O_{12}$.	P_4O_{12}''''.	I.	$K_2 \times 10^5$.
0	$0{\cdot}00784_5$	—	—	—	—	—	—	—	—	—	—	—
0·003330	$0{\cdot}00996_0$	0·06	0·03	0·39	19·47	13·23	5·10	2·01	1·23	0·07	0·03145	1·2
0·005809	$0{\cdot}01158_5$	0·12	0·16	0·35	22·69	22·96	4·23	3·75	1·63	0·28	0·04183	1·6
0·006932	$0{\cdot}01233_5$	0·15	0·22	0·33	24·19	27·36	3·90	4·63	1·74	0·34	0·04675	1·3
0·007194	$0{\cdot}01255_6$	0·16	0·21	0·33	24·63	28·41	3·79	4·89	1·78	0·32	0·04748	1·1

" *Hexametaphosphates* ".—*Sodium* " *hexametaphosphate* ". The formula $Na_6(PO_3)_6$ is commonly used for Graham's salt. It rests on doubtful evidence from freezing points, and the dubious preparation of derivatives such as $NaAg_5P_6O_{18}$ and $Na_2Ca_2P_6O_{18}$; the conductivity evidence is conflicting. On the other hand, the amorphous nature of the product, its very large and indefinite solubility in water, and the very high viscosity of its solutions all suggest that it is a high polymer, and Lamm (*Arkiv Kemi, Min. Geol.*, 1944, **17**, *A*, No. 25) has found molecular weights of about 13,000 in the ultra-centrifuge. Our conductivity measurements strongly support the view that the anion is of colloidal dimensions.

When sodium dihydrogen phosphate is fused, and then rapidly cooled, the " hexametaphosphate " produced is always contaminated, according to Jones (*Ind. Eng. Chem. Anal.*, 1942, **14**, 536), with a small amount of trimetaphosphate. This is probably because the reaction " hexametaphosphate " $\rightleftharpoons$ trimetaphosphate, which occurs at 625°, has time to proceed appreciably before the equilibrium is frozen. We removed the trimetaphosphate, and analysed our product, by the procedures suggested by Jones. The materials for which conductivity measurements are reported were shown in this way to be at least 99·92% pure. Other batches of fused material, used without further treatment, contained up to 10% or more of impurity, and gave conductivities that were the higher the greater the percentage impurity; this agrees with Jones's conclusions, since the trimetaphosphate has the higher conductivity of the two salts.

The densities at 25° of solutions of the pure product were determined, and may be expressed, up to an equivalent concentration $C = 0{\cdot}35$, by the equation $d_4^{25°} = 0{\cdot}99707 + 0{\cdot}078C$. The conductivities are tabulated herewith, and are plotted against the square-root of the equivalent concentration in Fig. 4, curve 1. In the more concentrated solutions, hydrolysis caused a slow drift in the resistance readings, and we have extrapolated back to zero time to correct, as far as possible, for this effect.

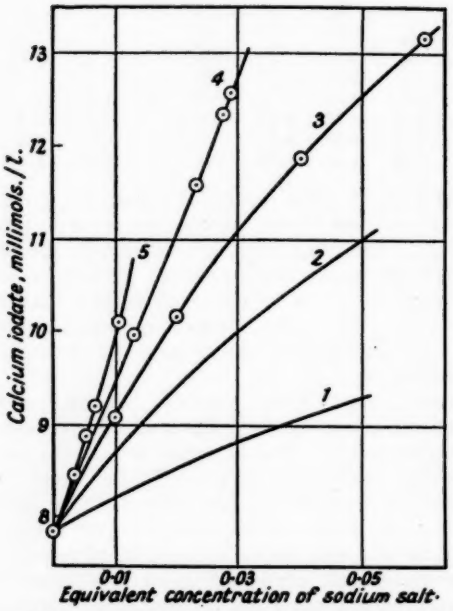
Conductivity of sodium " hexametaphosphate " solutions at 25°.

Batch.	$10^6\kappa_{H_2O}$.	10^4C.	$10^4C^{\frac{1}{2}}$.	Λ.	Batch.	$10^6\kappa_{H_2O}$.	10^4C.	$10^4C^{\frac{1}{2}}$.	Λ.
1	0·389	0·05641	23·8	87·8	1	0·457	2·7671	166·4	48·67
		0·10084	31·8	84·3			6·2650	250·3	42·57
		0·15195	39·0	80·8			8·7527	295·4	40·41
		0·22507	46·6	77·4			13·768	371·1	37·64
2	0·491	0·18911	43·5	81·3			18·988	435·8	35·88
		0·33125	57·6	73·0	1	0·519	8·8683	297·8	40·59
		0·43471	65·9	68·3			24·519	495·2	34·46
		0·57536	75·9	65·3			46·007	678·3	31·49
1	0·295	0·59768	77·3	64·05			74·602	863·7	29·73
		0·95087	97·5	59·30	2	0·480	92·287	960·7	29·83
		1·4687	121·2	55·10			192·42	1387	27·57
		2·0159	142·0	52·19			322·49	1796	26·56
		2·6882	163·9	49·71			443·13	2105	25·56
							640·44	2531	24·81

The conductivity curve is quite unlike that of a normal salt, and the slope in the most dilute solutions is far greater than would be expected even for a 1-6-valent salt. To provide a comparison with a colloidal electrolyte, the results of Ralston, Hoerr, and Hoffman (*J. Amer. Chem. Soc.*, 1942, **64**, 97) for octadecylamine hydrochloride at 60° are shown in curve 2. The similarity of the two curves will be evident.

Quimby points out that the ultracentrifuge results need not necessarily mean the linkage of a large number of PO_3 units through chemical bonds, since the loose association of numerous $(PO_3)_6$ units to form a micelle would lead to the same result. There seems little reason to expect such a micelle formation, but to test the point we pushed our conductivity measurements to the utmost practicable dilution. If the micellar explanation were correct, a "critical concentration for micelles" should exist at which a reversible dissociation into the simple hexameric units would occur. Such a critical concentration is clearly shown by octadecylamine hydrochloride at about $C^{\frac{1}{2}} = 0{\cdot}02$. For the "hexametaphosphate" there is no evidence for such a transition even at $C = 5 \times 10^{-6}$, which is the order of concentration in which it is employed in the "threshold" treatment of waters. Although this does not preclude the possibility of a critical concentration occurring at a still higher dilution, we can at least state that there is no evidence of the existence of units of ordinary molecular size at any attainable concentration, and that there remain, therefore, no experimental grounds for the hypothesis that a hexameric form of phosphoric acid exists.

FIG. 5.



Solubility at 25° of calcium iodate in solutions of: 1, *Sodium chloride;* 2, *sodium sulphate;* 3, *trimetaphosphate;* 4, *tetrametaphosphate;* 5, "*hexametaphosphate.*"

"*Hexametaphosphoric acid*". This was prepared, like the other acids, by ion exchange in an Amberlite column. The product was too unstable to give accurate conductivity data; the resistance readings decreased by about 1·5% in ten minutes. Three approximate measurements are shown in Fig. 4, and suggest that the acid has a conductivity curve similar to that found for the sodium salt.

Contradictory reports have been published about the strength of this acid. Treadwell and Leutwyler (*Helv. Chim. Acta*, 1938, **21**, 1450) state that two hydrogens (out of six) are strong, Salih (*Bull. Soc. chim.*, 1936, **3**, 1391) that four are strong, while Rudy and Schlosser (*Ber.*, 1940, **73**, 484) report that "all six hydrogens" ionise freely. The colloidal nature of the acid would account for the apparent strength varying with the concentration range studied, and this, together with the unstable nature of the acid, probably explains the conflicting results.

Interaction of "hexametaphosphate" with calcium ion. The solubilities of calcium iodate in sodium "hexametaphosphate" solutions are given below, and the collected solubility data are shown in Fig. 5. The "hexametaphosphate" results show an upward curvature; there is no basis for a quantitative treatment.

Solubility of calcium iodate in sodium "hexametaphosphate" solutions at 25°.

"Hexametaphosphate" (g.-equiv./l.)	0	0·003776	0·005455	0·006958	0·01065
$Ca(IO_3)_2$ (g.-mol./l.)	0·00784	0·00853	0·00886	0·00919	0·0101

Dimetaphosphates.—The preparation of sodium dimetaphosphate has been reported by Pascal and Rechid (*Compt. rend.*, 1933, **196**, 828), but the freezing-point evidence for the dimeric formula is not convincing. Travers and Chu (*ibid.*, 1934, **198**, 2100) gave an alternative method of preparation, and we have followed this method. The product, after several crystallisations from water–alcohol mixtures, gave the following conductivity results.

Equivalent conductivity at 25° of " sodium dimetaphosphate ".

10^4C	505·3	773·4	970·8	1290
$10^5C\sqrt{}$	2248	2781	3116	3592
Λ	126·75	125·15	124·25	122·83

When plotted, these points give a straight line which extrapolates to $\Lambda_0 = 133·5$. This would imply an unusually high mobility, 83·4, for the bivalent ion, and, moreover, the slope of the line is far greater than that predicted by Onsager's equation for a 1-2-valent salt. On comparing this curve with that for sodium trimetaphosphate, we find that the points fall on the curve with an error of not more than 0·1%, and we conclude that it is the trimetaphosphate which is prepared by Travers and Chu's method, and probably also, in a contaminated form, by that of Pascal and Rechid.

Monometaphosphates.—Work has been published by Beans and Kiehl (*J. Amer. Chem. Soc.*, 1927, **49**, 1878) on what is termed sodium monometaphosphate. This is discussed by Yost and Russell, who conclude that the salt is the trimetaphosphate, possibly contaminated with " hexametaphosphate ". This would be in keeping with the conductivity figures of Kiehl and Hill (*ibid.*, p. 123), which lie approximately midway between our results for the two salts. We have prepared a sample of Kiehl's salt, and submitted it to Jones's analytical procedure (*loc. cit.*). This also showed the product to be a mixture of sodium trimeta- and " hexameta "-phosphates, confirming Yost and Russell's suggestion.

The other claim to have prepared a monometaphosphate is that of Pascal (*Bull. Soc. chim.*, 1923, **33**, 1611), who obtained his product by the interaction of an ethyl phosphoric ester with sodium ethoxide. The evidence for a monomeric formula came from freezing-point measurements, but these could not be confirmed by Nylèn (*loc. cit.*), whose freezing points are almost identical with those for the trimetaphosphate. We followed the method of preparation given by Pascal, and obtained for our product the conductivities given in the following table.

Equivalent conductivity at 25° of Pascal's " monometaphosphate ".

10^4C	312·7	580·9	1036·5	1569·5	2280·4
$10^5C\sqrt{}$	1768	2410	3220	3962	4776
Λ	127·0	125·85	122·7	119·8	116·7

These points fall on a line almost parallel with our results for sodium trimetaphosphate, but about 2 units lower. It is likely therefore that this product also is mainly trimetaphosphate, possibly contaminated with orthophosphate; but all that can be said with certainty is that the conductivity results offer no support for the hypothesis that this method of preparation yields a monomeric (or dimeric) metaphosphate.

" *Metaphosphoric acid* ". The conductivity was examined of the product obtained by heating orthophosphoric acid at 400° for 5 hours. The results are tabulated herewith.

Conductivity at 25° of " ordinary " metaphosphoric acid.

10^4C	412·1	1032	1654	2161	3112
$10^4C\sqrt{}$	203	321	407	465	558
Λ	280·6	257·9	247·9	242·1	233·7

These figures do not correspond with any of the pure acids we have studied. They fall about midway between the curve for the " hexameta "-acid and those for the tri- and the tetra-acid. It might be possible to account for them by postulating a new, semi-strong, polybasic acid; but a much more probable explanation, which is in accord with Rechid's freezing-point data (*Compt. rend.*, 1934, **198**, 860), is that the product is a mixture.

Conclusions.

Yost and Russell, in their review of the literature on metaphosphates, conclude that if $(HPO_3)_n$ is written as a general formula for the metaphosphoric acids, there is evidence for the existence of the individuals in which n has the values 2, 3, 4, 6, and, possibly, 1; other writers, *e.g.*, Ephraim (" Inorganic Chemistry ", transl. by Thorne, 1926, 623), add 5, 8, 10, and 14 to the probable values of n. In our study of the soluble products of a variety of preparative methods, we have been able to identity only $H_3P_3O_9$, $H_4P_4O_{12}$, and a colloidal metaphosphoric acid (the former " hexametaphosphoric " acid) in which the value of n appears to be greater than 100 (cf. Lamm, *loc. cit.*). We conclude that the monomer is not stable, but tends to give polymers in which the unit group is $H^{\cdot}\left[-O-\overset{\overset{O}{|}}{\underset{\underset{O}{|}}{P}}-\right]'$; such polymers may be closed rings of three

units (the relatively stable trimetaphosphates), or of four units (the tetrametaphosphates, with a more limited range of stability), or may be very long chains of colloidal dimensions. In addition to these, there are the insoluble metaphosphates which we have not examined, and which presumably have continuous structures such as are found in the silicates.

Experimental.

The equipment used for the conductivity measurements, and the conductivity-water still, were similar to those described in earlier papers (cf. Davies, *J.*, 1937, 432). Measurements were made at frequencies of 1000 and 2500 cycles, and a cathode-ray oscillograph showed that the oscillator was producing a good sine wave. The cell used for the more concentrated solutions was standardised by means of Jones and Bradshaw's 0·01D-potassium chloride solution, and had a constant of 0·13103 ± 0·03%. For more dilute solutions a Hartley–Barrett cell (constant: 0·045960 ± 0·02%) was standardised against potassium chloride solutions of concentrations below 0·001N, using the interpolation formula $\Lambda = 149{\cdot}92 - 93{\cdot}85C^{\frac{1}{2}} + 50C$ (Davies, *loc. cit.*).

The solubility measurements were made in the manner described in previous papers (*J.*, 1935, 1416; 1938, 273).

Sodium Trimetaphosphate.—Sodium dihydrogen phosphate was prepared in the following manner. A slight excess of "AnalaR" phosphoric acid was added to a concentrated solution of "AnalaR" disodium phosphate in distilled water. Crystallisation was induced by addition of alcohol and cooling in a refrigerator. The crystals were recrystallised twice in a similar manner, being filtered each time on to a sintered-glass filter and washed with dilute aqueous alcohol. The trimetaphosphate was formed by Jones's method (*loc. cit.*), the samples being heated in a platinum crucible in an electric furnace.

Sodium Tetrametaphosphate.—Pure cupric oxide was heated in a platinum dish with 5% excess of "AnalaR" phosphoric acid according to Warschauer's method (*loc. cit.*). The cupric tetrametaphosphate was ground to a powder and a slight excess of "AnalaR" sodium sulphide solution stirred with it, and the resulting cupric sulphide filtered off on a sintered-glass crucible. The sodium salt was precipitated from the filtrate by adding alcohol and cooling. Recrystallisations were effected first from distilled water and alcohol, traces of sulphur being filtered off by means of a fine paper, and finally two recrystallisations were made from conductivity water and pure alcohol. The first sample was recrystallised five times and the second eight times. The crystals were dried over phosphoric oxide in a vacuum, and the water content found, at the time of taking a sample for conductivity, by ignition in a platinum crucible.

Sodium "Hexametaphosphate".—Sodium dihydrogen phosphate, prepared as above, was fused at 900° in a platinum dish in a gas muffle furnace, and then cooled rapidly by ice-water. The product was dissolved in water, and the solution slowly added to a solution of "AnalaR" silver nitrate with rapid stirring. The coagulum of silver "hexametaphosphate" was filtered on to a sintered-glass funnel and well washed with water. It was then suspended in about a litre of water, stirred mechanically, and an excess of "AnalaR" sodium chloride solution added. After the silver chloride had been filtered off, alcohol was added slowly with vigorous stirring, until about 20% was present. Slow addition of the alcohol is important, otherwise no separation occurs. The "hexametaphosphate" separated out in globules of viscous liquid which rapidly collected at the bottom of the beaker. The supernatant liquor was decanted off, the coagulum washed several time with 10% aqueous alcohol, and then redissolved in distilled water. Separation was carried out three times more by addition of alcohol, the last two being from solution in conductivity water. The oil was partially dehydrated by transference to a platinum dish and application of a vacuum pump for 5 hours. After a final drying in a vacuum over phosphoric oxide, it was obtained as a porous brittle glass containing about 9% of water. The exact amount was determined each time by ignition of samples. Analysis for other forms of phosphate by Jones's method (*loc. cit.*) indicated that not more than 0·08% of these were present.

Tri-, Tetra-, and "Hexa"-metaphosphoric Acids.—A column of Amberlite I.R-100 of approximately 40 g. dry weight (about four times that required) was formed in a 1-cm. hard-glass tube. After hydrogenation with acid, it was washed with distilled water and then with conductivity water. Tests showed that the specific conductivity of the water only rose to 2 or 3 gemmhos. This meant a negligible error in the conductivity measurements on the acid, since only a small amount of the stock solutions of these were used. About 1·5 g. of the sodium salt in about 400 ml. of conductivity water were passed through this column, the rate being adjusted so that the operation took about an hour. The resulting stock solutions were tested for sodium by means of zinc uranyl acetate (Vogel, "Quantitative Inorganic Analysis"), and comparison with a blank test on the reagent indicated that the conversion was complete to within 0·2%, the blank being equivalent to this amount. The concentrations of the stock solutions were found by weighing out portions, hydrolysing by nitric acid (Jones, *loc. cit.*), and carrying out a double precipitation as magnesium ammonium phosphate (Vogel, *op. cit.*). The ignition to magnesium pyrophosphate at 1100° was effected on sintered-porcelain crucibles. Duplicate estimations were made on each sample. For the trimetaphosphoric acid these agreed to within 0·05%, 0·2%, and 0·03% for the three runs respectively, for the tetrametaphosphoric acid to within 0·1%, 0·03%, and 0·02%, and within 0·1% for the "hexametaphosphoric" acid.

We are indebted to the Resinous Products and Chemical Company, of Philadelphia, for the Amberlite used in the preparations.

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[*Received, May 21st*, 1948.]

95. *The Condensed Phosphoric Acids and Their Salts. Part II. Pyrophosphates.*

By C. B. Monk.

The third and the fourth dissociation constant of pyrophosphoric acid at 25° have been estimated from pH measurements on solutions of the sodium salts and the acid, association between the sodium and pyrophosphate ions being taken into consideration. Conductivity measurements of dilute solutions of sodium pyrophosphate at 25° are reported, and corrections applied for hydrolysis and possible ion-associations resulting from hydrolysis.

Three series of values are given in the literature for the third and the fourth dissociation constant of pyrophosphoric acid. Abbott and Bray (*J. Amer. Chem. Soc.*, 1909, **31**, 729) give $2{\cdot}9 \times 10^{-7}$ and $3{\cdot}6 \times 10^{-9}$, respectively, at 18°; Kolthoff and Bosch (*Rec. Trav. chim.*, 1928, **47**, 826) give $2{\cdot}1 \times 10^{-7}$ and $4{\cdot}06 \times 10^{-10}$ at 18°, and Morton (*J.*, 1928, 1401) gives $2{\cdot}1 \times 10^{-7}$ and $1{\cdot}31 \times 10^{-10}$ at 30°. Abbott and Bray's results, which were based on distribution studies of the hydrolysis of pyrophosphate salts, are markedly different from the others because interionic effects were unrecognised at that time and consequently were not included in the calculations. The last two series were averaged from pH measurements ending at rather high concentrations and therefore needed rather large activity corrections. A possible modification in computing the dissociation constants is to take into consideration the extent to which such ions as NaP_2O_7''' and $NaHP_2O_7''$ exist in solution. This approach has been taken in the present paper, the treatment being confined to relatively dilute solutions. The extensive studies which have been made on electrolytes in solution indicate that the 1 : 1 and 1 : 2 valency types of salts show complete or almost complete dissociation. With the higher valency types there is strong evidence to show that this is not the case. As a broad generalisation the extent of association for these cases is of the same order for any particular valency type of salt, and use has been made of this for making minor corrections to the data given here.

The Third Acid Dissociation Constant.—A stock solution of pyrophosphoric acid was prepared from the sodium salt by the ion-exchange method mentioned in Part I (preceding paper). The cell used for the pH measurements contained conductivity water which was kept under a stream of carbon dioxide-free air. Conductivity measurements on some of the water indicated that the amount of carbon dioxide was negligibly small. A convenient amount of the acid stock solution was admitted, followed by suitable amounts of carbonate-free sodium hydroxide. The concentrations are given in the table below.

K_3 for pyrophosphoric acid at 25°.

Concentrations ($\times 10^4$).

	(*a*).	(*b*).	(*c*).		(*a*).	(*b*).	(*c*).
$H_4P_2O_7$	4·16	4·16	4·16	$I \times 10^4$	14·5	16·5	19·1
NaOH	8·99	9·67	10·51	pH	5·78	6·15	6·50
HP_2O_7'''	0·67	1·35	2·19	$K_3 \times 10^7$	2·58	2·72	2·77
$H_2P_2O_7''$	3·49	2·81	1·97				

Ion association between the sodium ions and the pyrophosphate ions is small enough to be ignored in the present case, so the amounts of HP_2O_7''' and $H_2P_2O_7''$ can be obtained from the relations $m = [HP_2O_7'''] + [H_2P_2O_7'']$, and $4m - [NaOH] = [HP_2O_7'''] + 2[H_2P_2O_7'']$, where m is the pyrophosphate molarity. The third acid dissociation constant, K_3, was calculated from the expression

$$\log K_3 = -\mathrm{pH} + \log\{HP_2O_7'''\}/\{H_2P_2O_7''\} + \log f_3/f_2$$

where f_2 and f_3 are the ion-activity coefficients for bi- and ter-valent ions, respectively. The latter were obtained by use of Davies's modified Debye mean ionic-activity coefficient formula (*J.*, 1938, 2093). The results of the calculations are given in the table, and the average of K_3 is $2{\cdot}7 \times 10^{-7}$.

The Fourth Acid Dissociation Constant.—The method used by Kolthoff and by Morton (*locc. cit.*) was employed, *i.e.*, mixing sodium pyrophosphate and hydrochloric acid in 2 : 1 molecular proportions. As for the K_3 measurements, the carbon dioxide present in the water was calculated from conductivity measurements on the same batch of water. Since the solutions were of high pH, the carbon dioxide became converted into bicarbonate and carbonate. The first of these was calculated from the first dissociation constant for carbonic acid, *i.e.*, $4{\cdot}45 \times 10^{-7}$ (Harned and Davis, *J. Amer. Chem. Soc.*, 1943, **65**, 2030), and the carbonate obtained by difference.

In the solutions under consideration, interaction between the sodium ions and the pyrophosphate ions to form NaP_2O_7''', and to a lesser extent $Na_2P_2O_7''$ and $NaHP_2O_7''$, is to be expected. The evidence for the presence of NaP_2O_7''' is, first, that the analogous cases of sodium tetrametaphosphate (Part I, *loc. cit.*) and potassium ferrocyanide (Davies, *J. Amer. Chem. Soc.*, 1937, **59**, 1760) both show this type of association, and for these the dissociation constants of the associated ions are 0·009 and 0·005, respectively. Further evidence was also supplied by the conductivity measurements described later. From the conductivity figures obtained after correction for hydrolysis, an approximate value of 0·002 was obtained for the dissociation constant of the NaP_2O_7''' ion. Accordingly, a dissociation constant of 0·005 was used in the present calculations for the acid dissociation constant. More accurate hydrolysis corrections to the conductivity measurements after the present work was completed justified this chosen value, since the final calculation gave a dissociation constant of 0·0045 for NaP_2O_7'''. In the cases of the other two ions, *i.e.*, $Na_2P_2O_7$ and $NaHP_2O_7$, a value of 0·05 was assumed to be the order of their dissociation constants. This is a round average of the available data. Thus in Part I it was shown that the corresponding sodium trimetaphosphate ion has a value of 0·068, and in addition potassium ferricyanide and hexamminocobaltic chloride have the values of 0·04 and 0·03 respectively (calculated from the data of Hartley and Donaldson, *Trans. Faraday Soc.*, 1937, **33**, 465), while potassium cobalticyanide averages 0·034 (James, Ph.D. Thesis, London, 1947). In any case the concentrations of these two species are quite small, so any uncertainty in the assumed dissociation constant value cannot give rise to serious errors.

The expressions used for calculating the various ionic concentrations are $[HCl] + 2[CO_2] = [HP_2O_7'''] + [HCO_3'] + [NaHP_2O_7'']$ and $m - [HCl] = [P_2O_7''''] + [NaP_2O_7'''] + [Na_2P_2O_7'']$, where the carbon dioxide refers to that present in the water before the addition of sodium pyrophosphate of molarity m and hydrochloric acid of approximately $0{\cdot}5m$. These two expressions follow from a consideration of the distribution of the hydrogen ions, and from the difference between these concentrations and the total pyrophosphate molarity. In addition the dissociation constant expressions for NaP_2O_7''', $Na_2P_2O_7''$ and $NaHP_2O_7''$ are also required. An approximation method was used, first leaving out of account the intermediate ions, then using the resulting concentrations of P_2O_7'''', HP_2O_7''', and Na^+ and the ionic strength to find first values of the other species. The activity coefficients were calculated as in the case of K_3. Continuation along these lines led to the constant values shown below. The fourth acid dissociation constant, K_4, was evaluated from

$$\log K_4 = -\mathrm{pH} + \log\{P_2O_7''''\}/\{HP_2O_7'''\} + \log f_4/f_3$$

where f_3 and f_4 are the mean ionic activity coefficients for ter- and quadri-valent ions respectively, calculated as above. The results are shown in the table. The average value of K_4 is

K_4 for pyrophosphoric acid at 25°.

Concentrations ($\times 10^4$).

	(*a*).	(*b*).	(*c*).	(*d*).	(*e*).	(*f*).	(*g*).
$Na_4P_2O_7$	5·23	8·21	8·85	9·00	16·43	16·50	23·40
HCl	2·56	4·11	4·43	4·47	8·22	8·25	11·70
Na^+	20·37	31·64	34·04	34·60	62·25	62·64	87·71
P_2O_7''''	2·06	3·03	3·28	3·29	5·36	5·25	6·99
NaP_2O_7'''	0·48	0·97	1·11	1·13	2·63	2·72	4·32
$Na_2P_2O_7''$	0·01	0·04	0·04	0·05	0·17	0·17	0·35
HP_2O_7'''	2·59	4·07	4·29	4·36	7·75	7·86	10·86
$NaHP_2O_7''$	0·07	0·15	0·17	0·18	0·50	0·50	0·87
HCO_3'	0·05	0·09	0·03	0·05	0·03	0·09	0·03
CO_3''	—	0·01	—	—	—	0·01	—
$I \times 10^3$	4·21	6·52	7·00	7·11	12·6	12·6	17·7
pH	9·312	9·197	9·201	9·269	9·134	9·125	9·079
$K_4 \times 10^{10}$	2·39	2·62	2·61	2·19	2·25	2·26	2·15

$2{\cdot}4 \pm 0{\cdot}2 \times 10^{-10}$. A slight drift in these values occurs with increasing ionic strength, which is probably due to the assumed dissociation constant of 0·05 (above) not being quite exact, and to the activity coefficient expression being a little inaccurate in the present case.

The Conductivity of Sodium Pyrophosphate Solutions at 25°.—Abbott and Bray (*loc. cit.*) measured the conductivity of sodium pyrophosphate solutions at 18°, but these results are based on an obsolete method of determining the cell constant. Other measurements by Watkins and Jones (*J. Amer. Chem. Soc.*, 1915, **37**, 1628) at 25° are expressed in Siemens units. In the

present work fresh results are recorded and corrected, as far as possible, for hydrolysis. In addition, corrections have been made for the ion-associations which take place between the products of hydrolysis. Finally, the corrected results have been used to derive the dissociation constant of the ion NaP_2O_7'''. The concentration range $C = 0{\cdot}00045$ to $0{\cdot}003$ was studied. The resistance readings showed a slow drift with time (about 0·1% per hour); so far as possible this was allowed for by taking time measurements and extrapolating back to the time of addition of the stock solution.

Since extensive hydrolysis occurs, and since ion-association amongst the products of hydrolysis must be taken into consideration, complex corrections are necessary to obtain the true conductivities. The equilibria to be taken into account are: $P_2O_7'''' + H_2O \rightleftharpoons HP_2O_7'''$; $2P_2O_7'''' + H_2CO_3 \rightleftharpoons 2HP_2O_7'''$; $P_2O_7'''' + H_2CO_3 \rightleftharpoons HP_2O_7''' + HCO_3'$; $P_2O_7'''' + Na^{\cdot} \rightleftharpoons NaP_2O_7'''$; and $HP_2O_7''' + Na^{\cdot} \rightleftharpoons NaHP_2O_7''$. Letting the concentrations be represented by $a = HCO_3'$, $b = CO_3''$, $d = NaP_2O_7'''$, $e = NaHP_2O_7''$, $y = OH'$, and m the pyrophosphate molarity, we then have

$$K_h = \frac{K_w}{K_4} = \frac{\{OH'\}\{HP_2O_7''\}}{\{P_2O_7''''\}} = \frac{y(y + a + 2b - e)f_1f_3}{(m - y - a - 2b - d)f_4}$$

In this, K_4, the fourth dissociation constant of pyrophosphoric acid, is $2{\cdot}4 \times 10^{-10}$ (see above), K_w is $1{\cdot}0 \times 10^{-14}$ (Harned and Hamer, *J. Amer. Chem. Soc.*, 1933, **55**, 1924); and f_1, f_3, and f_4 are the ion activity coefficients for uni-, ter-, and quadri-valent ions, respectively, calculated as before. The carbon dioxide was calculated from the specific conductivity of the water. To find the various concentrations, the following procedure was used. First, ion-association corrections were omitted and a preliminary value of y obtained. The resulting value, together with the calculated ionic strength, was then used to calculate first values of a, d, and e, the dissociation constants referred to in connection with the K_4 calculations being used. The difference between the carbon dioxide and a gave the concentration of b. The new ionic strength was used for calculating second approximations, and so on. The constant values eventually obtained are given in Table I.

TABLE I.

Conductivity of sodium pyrophosphate at 25°. [Ion concentrations (× 10^5).]

Run.....	(*a*).	(*b*).	(*c*).	(*d*).	(*e*).	(*f*).	(*g*).	(*h*).	(*i*).
C	46·13	50·17	54·50	73·35	83·80	133·24	199·99	260·87	316·02
$Na^{\cdot}$	45·7	49·6	53·8	72·2	82·3	129·6	192·4	149·2	300·0
P_2O_7''''	6·22	6·99	7·78	11·08	12·99	21·66	33·07	43·08	51·81
HP_2O_7'''	4·84	4·99	5·18	6·06	6·41	7·99	9·46	10·48	11·22
OH'	4·36	4·69	4·98	5·87	6·30	7·96	9·52	10·62	11·43
NaP_2O_7'''	0·43	0·52	0·62	1·13	1·47	3·51	7·23	11·34	15·58
$NaHP_2O_7''$	0·04	0·04	0·05	0·07	0·08	0·15	0·24	0·32	0·40
HCO_3'	0·39	0·26	0·19	0·18	0·13	0·12	0·12	0·12	0·11
CO_3''	0·06	0·04	0·03	0·04	0·03	0·03	0·03	0·03	0·04
$I \times 10^4$	9·89	10·82	11·80	16·03	18·39	29·40	44·12	57·35	69·17

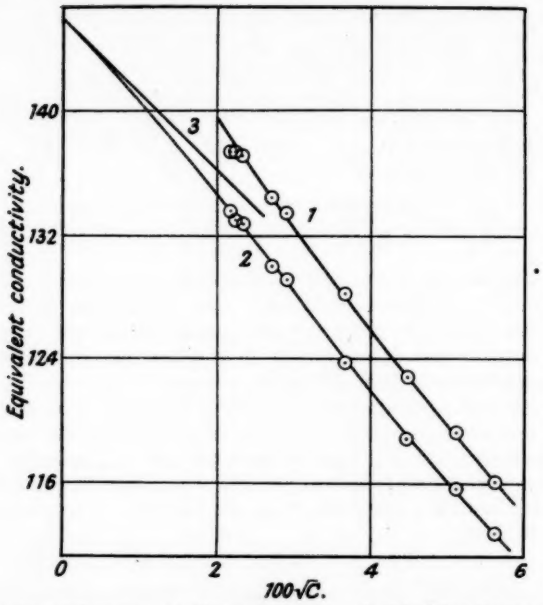
Corrections to the conductivity measurements were then applied. These were effected by regarding the solutions as mixtures of $Na_4P_2O_7$, $Na_3HP_2O_7$, NaOH, $NaHCO_3$, and Na_2CO_3. That is,

$$4m\Lambda_{obs.} = 4Na_4P_2O_7\Lambda_{Na_4P_2O_7} + 3Na_3HP_2O_7\Lambda_{Na_3HP_2O_7} + 2NaHP_2O_7''\Lambda_{Na_3,NaHP_2O_7} + 2Na_2CO_3\Lambda_{Na_2CO_3} + NaHCO_3\Lambda_{NaHCO_3} + NaOH\Lambda_{NaOH}$$

For the conductivity of the sodium hydroxide, Darken and Meier's data (*J. Amer. Chem. Soc.*, 1942, **64**, 621) were taken. Those of $NaHCO_3$ and Na_2CO_3 are given in a further paper (this vol., p. 429). In the case of $Na_3HP_2O_7$, the conductivity was calculated from Abbot and Bray's data (*loc. cit.*), *viz.*, $\Lambda_0 = 102{\cdot}9$ at 18°. The mobility of the sodium ion at this temperature is 43·4 (Davies, "Conductivity of Solutions", Chap. XVII), and is 50·1 at 25° (Shedlovsky, MacInnes, and Longsworth, *J. Amer. Chem. Soc.*, 1932, **54**, 2758). So if a temperature coefficient of 0·022 is used (Davies, *op. cit.*), the resulting Onsager equation for $Na_3HP_2O_7$ at 25° is $\Lambda_0 = 120{\cdot}0 - 190{\cdot}5I^{\frac{1}{2}}$. The equation for the part of this salt which is not fully dissociated can be obtained by the methods used before (cf. sodium trimetaphosphate, Part I), and is $\Lambda = 96{\cdot}7 - 136{\cdot}4I^{\frac{1}{2}}$. The conductivities calculated from these expressions, using the values of I given in Table I, together with the concentrations given in this table, permit the conductivity of sodium pyrophosphate to be calculated from the mixture rule formulated above. The fraction of sodium pyrophosphate which is not fully dissociated has been included with the part which

is completely ionised. This is because it is required to evaluate the experimental dissociation constant of the NaP_2O_7''' ion from the corrected conductivity data. The reason for calculating an approximate value of this ion in Table I was to obtain a truer value of I for use in the conductivity equations of the other species, and for calculating the concentrations of these. The corrected conductivity measurements are shown in Table II, and the curve in the figure.

Equivalent conductivity of sodium pyrophosphate solutions at 25°.



1, *Experimental curve.* 2, *Corrected curve.* 3, *Limiting Onsager slope.*

Extrapolation of the calculated conductivity curve leads to $\Lambda_0 = 146{\cdot}0$, so the mobility of the pyrophosphate ion is 95·9. The discrepancy between the curve and the theoretical Onsager equation, as discussed in Part I (*loc. cit.*), may be used to estimate the extent of association

TABLE II.

Conductivity of sodium pyrophosphate at 25° (corrected data).

Run.	$10^6\kappa_{H_2O}$.	10^6C.	$10^5C^{\frac{1}{2}}$.	$\Lambda_{obs.}$.	$\Lambda_{Na_4P_2O_7}$.	α.	K.
a	0·480	461·34	2148	137·40	133·65	0·929	0·0043
b	0·382	501·72	2240	137·35	133·06	0·924	0·0043
c	0·311	545·03	2335	137·19	132·78	0·920	0·0044
d	—	733·45	2708	134·50	130·02	0·899	0·0043
e	0·253	838·05	2895	133·52	129·14	0·895	0·0046
f	—	1332·4	3650	128·22	123·80	—	—
g	—	1999·9	4472	122·88	118·94	—	—
h	—	2608·7	5108	119·35	115·74	—	—
i	—	3160·2	5622	116·24	112·82	—	—

between sodium and pyrophosphate ions, the process being analogous to that used for sodium tetrametaphosphate. The Onsager equation for the full stage of dissociation is $\Lambda = 146{\cdot}0 - 261{\cdot}0I^{\frac{1}{2}}$. If $\frac{3}{4}$ of 95·9 is taken as the mobility of the NaP_2O_7''' ion, the Onsager equation for the dissociation $Na_4P_2O_7 \rightleftharpoons 3Na^{\cdot} + NaP_2O_7'''$ is $\Lambda = 122{\cdot}0 - 192{\cdot}0I^{\frac{1}{2}}$. So if α is the fraction of sodium pyrophosphate which completely ionises, combination of the two equations leads to

$$\Lambda = 91{\cdot}5 \times \alpha(54{\cdot}5 - 117{\cdot}0I^{\frac{1}{2}}) - 144{\cdot}0I^{\frac{1}{2}}$$

The dissociation constant for the equilibrium $NaP_2O_7''' \rightleftharpoons Na + P_2O_7''''$ can thus be obtained from

$$K = \{Na^{\cdot}\}\{P_2O_7''''\}/\{NaP_2O_7'''\} = (3 + \alpha)\alpha m f_{\pm}^2/(1 - \alpha)$$

where $\log f_{\pm} = -0{\cdot}509I^{\frac{1}{2}}$. Calculations were confined to the more dilute regions, since, strictly

the Onsager equation is only reliable where the difference between Λ_0 and Λ is about 10% of Λ_0. The results are shown in Table II, and the average value of the dissociation constant is about 0·0045, thus substantiating the assumed figure of 0·005 used in the calculations for the fourth acid dissociation constant.

EXPERIMENTAL.

Sodium pyrophosphate was made by fusion, at 1100° in a platinum dish, of " AnalaR " disodium hydrogen phosphate which had been twice recrystallised from conductivity water. The cell used for the pH measurements was a seasoned round-bottomed Pyrex flask. The bung to this contained an entrance tube for the addition of the stock solutions, a tube for the introduction of carbon dioxide-free air, a " Cambridge " glass electrode, and a dipping silver–silver chloride electrode. The last was contained in a potassium chloride liquid-junction tube fitted with a ground-glass cap. The electrode was made by Brown's method (*J. Amer. Chem. Soc.*, 1934, **56**, 646). Temperature control was maintained by an oil-bath at 25° ± 0·01°. The cell was swept out with the washed air before being filled with conductivity water from a stock solution of known value. A " Cambridge " bench-model pH meter was used, and calibrated with suitable buffers (Acree, Hamer, and Pinching, *J. Res. Nat. Bur. Stand.*, 1945, **35**, 47; Manov, De Lollis, and Acree, *ibid.*, 1944, **33**, 287; Manov, De Lollis, Linvall, and Acree, *ibid.*, 1945, **36**, 543). Details concerning the conductivity measurements have been given in Part I.

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[*Received, May 21st*, 1948.]

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96. *The Condensed Phosphoric Acids and Their Salts. Part III. Polyphosphates, and General Summary.*

By C. B. MONK.

Conductivity measurements on sodium tripolyphosphate ($Na_5P_3O_{10}$) have been made and analysed. The results support the formula. The mobility of the anion, after making an approximate hydrolysis correction, is found to be 109, and the dissociation constant of the $NaP_3O_{10}^{""}$ ion is regarded as being about 0·003.

COMPOUND formation between pyrophosphate and metaphosphate by heat treatment has been the subject of much investigation. Much confusion existed as to the exact number and nature of the compounds formed owing to the difficulty of analysing the products. Because of the industrial importance in water-softening, study of the system has been accelerated in recent years, and thermal analyses, together with microscope methods of examination (Andress and Wüst, *Z. anorg. Chem.*, 1938, **237**, 113; Partridge, Hicks, and Smith, *J. Amer. Chem. Soc.*, 1941, **63**, 454; Morey and Ingerson, *Amer. J. Sci.*, 1944, **242**, 1), have neatly clarified the position. The results show that sodium tripolyphosphate, $Na_5P_3O_{10}$, produced by fusion of equimolecular amounts of sodium pyrophosphate and any of the sodium metaphosphates, is the only stable compound formed by thermal methods. Any other ratios of the constituents produce this compound mixed with the excess component. Confirmation of this has been supplied by polarographic work (Campbell, *J. Amer. Chem. Soc.*, 1947, **69**, 109).

There is the point to consider as to whether or not the tripolyphosphate is polymerised. Freezing-point depressions and application of the Ostwald rule are said to support the simple formula (Bonneman-Bémia, *Ann. Chim.*, 1941, **16**, 395), but, as pointed out in Part I (this vol., p. 413), these methods are open to objection. Bonneman-Bémia (*loc. cit.*) reported a series of conductivity measurements at 25°, but they are much lower than would be expected for this compound. Comparison with the figures which we obtained indicated, as far as can be ascertained, that they were based on the hexahydrate (the product obtained by crystallisation from aqueous solution), instead of on the anhydrous salt.

Sodium Tripolyphosphate.—Calculated amounts of sodium trimetaphosphate and sodium pyrophosphate, prepared as described in Parts I and II, were intimately mixed and heated in a platinum dish in a similar fashion to that described by Jones (*Ind. Eng. Chem. Anal.*, 1942, **14**, 536). Unfortunately, this does not produce a pure compound: Jones's analytical method (*loc. cit.*) indicates that up to 10% of the constituents may be uncombined. According to Quimby (*Chem. Reviews*, 1947, **40**, 141) the compound decomposes as it melts at 622°, recombination depending on the manner of cooling. He considers that a higher degree of combination could be effected by prolonged heating around 500°. However, the analytical methods themselves are not entirely satisfactory; Bell (*Ind. Eng. Chem. Anal.*, 1947, **19**, 97) has given a method which he claims to be better than that of Jones (*loc. cit.*), but the work is still being developed. An attempt at purification was made by dissolving a sample in water and fractionally precipitating

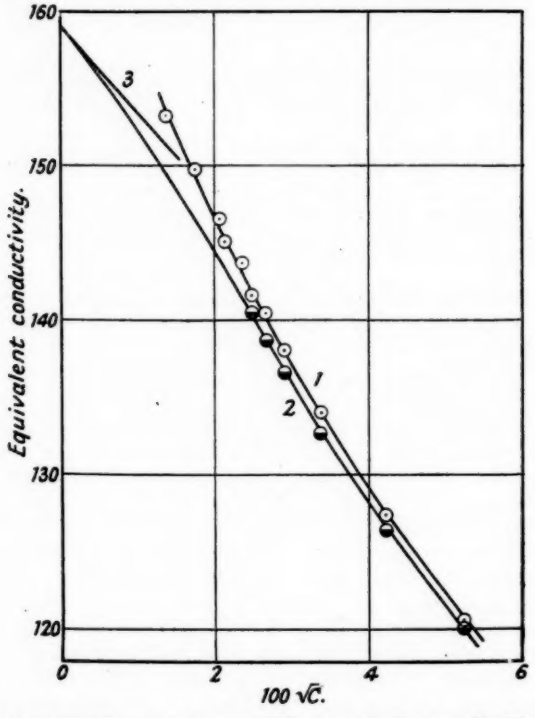
it by alcohol. This, as judged by analysis and by comparison of the conductivity with that of the untreated portion, does not assist in separating the impurities. Campbell (*loc. cit.*) came to a similar conclusion. The slight drift in the resistance readings was corrected as before (Part II). The data are shown in the first table and in the figure. Run 2 was made with the sample obtained by dissolution in water and precipitation with alcohol.

Conductivity of sodium tripolyphosphate at 25°.

Run.	$10^6\kappa_{H_2O}$.	10^6C.	$10^5C\frac{1}{2}$.	Λ (obs.).	Λ (corr.).	Run.	$10^6\kappa_{H_2O}$.	10^6C.	$10^5C\frac{1}{2}$.	Λ (obs.).	Λ (corr.).
1	0·243	452·33	2127	145·0	—	2	0·409	194·0	1393	153·1	—
		623·63	2497	141·5	—			305·1	1747	149·7	—
		910·17	2902	137·9	136·5			428·2	2069	146·5	—
		1137·7	3375	133·9	132·6			556·2	2358	143·5	140·4
		1776·5	4215	127·4	126·4			709·8	2664	140·3	138·6
		2749·6	5244	120·6	120·1						

Hydrolysis, the presence of uncombined constituents, and the products of ion-association due to these, preclude any exact treatment of the data. An approximate analysis has been

Equivalent conductivity of sodium tripolyphosphate at 25°.



1, *Experimental curve*; **2**, *corrected curve*; **3**, *Onsager limiting slope.*

attempted along the following lines. Leaving out of account ion-association due to the by-products, and any change in the conductivity due to uncombined constituents, and only considering the effects of hydrolysis, we may write

$$1000\kappa = 5\Lambda_a[a] + \Lambda_b[b] + 4\Lambda_c[c]$$

where $a = Na_5P_3O_{10}$, b = NaOH, and $c = Na_4HP_3O_{10}$; whence

$$100\Delta\kappa = [OH'](5\Lambda_a - \Lambda_b - 4\Lambda_c)$$

where $\Delta\kappa$ is the change in the specific conductivity due to hydrolysis. Accordingly $\Lambda_a = \Lambda_{obs.} + 1000\Delta\kappa/C$, C being the equivalent concentration. The pH of a 1% solution is 9·4 (Bell, *loc. cit.*), so we can take $[OH'] = 2{\cdot}5 \times 10^{-5}$ (it will not alter significantly with concentration). The $\Delta\kappa$ values can be deduced by an approximation method. First, the observed conductivity can be taken for Λ_a; Λ_b is known (Darken and Meier, *J. Amer. Chem. Soc.*, 1942,

64, 621), and for Λ_c, the conductivity of sodium pyrophosphate may be taken as a reasonable basis (Part II). These give results leading to $\Lambda_0 = 154$ for $Na_5P_3O_{10}$, thus giving 104 as the mobility of the anion. As a second approximation we can take 4/5 of this for the mobility of the $HP_3O_{10}^{''''}$ ion, and, using the Onsager equation, derive truer values of Λ_c at each concentration, thereby obtaining a second value of Λ_0 for $Na_5P_3O_{10}$. Continuation along these lines eventually leads to constant figures, giving $\Lambda_0 = 159{\cdot}0$ for $Na_5P_3O_{10}$. The corrected figures are given in the table and plotted in the graph. The theoretical Onsager equation based on the assumption that this is a 1 : 5-valent salt is $\Lambda = 159{\cdot}0 - 323I^{\frac{1}{2}}$. The slope corresponding to this is shown in the graph and approximates to that of the corrected conductivity curve. If the substance were polymerised we would expect a much greater discrepancy between the two slopes. Furthermore, if it were heavily polymerised we would expect the corrected and experimental curves to be much lower in value, as found in the case of sodium " hexametaphosphate ". The mobility of the $P_3O_{10}^{''''}$ ion is 109, as compared with 95·9 for the $P_2O_7^{''''}$ ion (Part II); this therefore follows the general rule that the higher the valency of the anion, the higher the mobility.

As discussed in the other Parts of this series, the discrepancy between the corrected curve and the theoretical Onsager curve may be used to calculate the extent of ion-association. Taking $\frac{4}{5}$ of 109 for the mobility of the $NaP_3O_{10}^{''''}$ ion, the Onsager equation for this stage of the dissociation is $\Lambda = 137{\cdot}3 - 252I^{\frac{1}{2}}$, so if α is the fraction which fully dissociates, we have

$$\Lambda = 109{\cdot}8 - \alpha(49{\cdot}0 - 121I^{\frac{1}{2}}) - 202I^{\frac{1}{2}}$$

The treatment is necessarily approximate because of the restrictions mentioned earlier, so it is not worth while making detailed calculations for the dissociation constant. One point only has been considered, *i.e.*, for $\Lambda_{(obs.)} = 140{\cdot}3$, for which a K value of 0·0027 is obtained. There are no other salts with which to compare this at present, although it is of the order expected for a 1 : 5-valent type.

Tetrapolyphosphate.—Earlier claims for the preparation of sodium tetrapolyphosphate, $Na_6P_4O_{13}$, by fusion methods (Fleitmann and Henneberg, *Annalen*, 1848, **65**, 304) can no longer be accepted in view of the work of Partridge, *et al.* (*loc. cit.*). This does not preclude the possibility, however, of preparing the tetrapolyphosphate in aqueous solution. Hatch (U.S.P. 2,365,190; Dec. 19, 1944) and Bell (*Ind. Eng. Chem.*, 1947, **39**, 137) have shown that tripolyphosphate is the first product of hydrolysis when sodium trimetaphosphate is treated with 1% sodium hydroxide solution at 100°. It may therefore be suggested that sodium tetrametaphosphate, the existence of which was confirmed in Part I, may give rise in an analogous way to tetrapolyphosphate when subjected to alkaline hydrolysis. The major difficulty in investigating this lies in the chemical analysis, the limitations of which were referred to earlier.

Summary of Results.—The new data obtained in this series of papers are collected below.

Mobilities at 25° of complex phosphate ions.

Ion.	Trimeta-.	Tetrameta-.	Pyro-.	Tripoly-.
Mobility	83·59	93·69	95·9	109

Dissociation constants of the acids and their sodium and calcium salts.

	Acid.	Na salt.	Ca salt.		Acid.	Na salt.
Trimeta-	0·0083	0·068	0·00033	Pyro-	K_2 2·7 × 10^{-7}	—
Tetrameta-	0·0018	0·009	K_1 0·0022		K_4 2·4 × 10^{-10}	0·0045
			K_2 1·3 × 10^{-5}	Tripoly-	—	0·003

The author is indebted to Professor C. W. Davies for his interest and assistance.

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[*Received, May 21st*, 1948.]

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97. *The Conductivity of Sodium Carbonate Solutions at 25°.*

By C. B. MONK.

Hydrolysis corrections have been applied to some conductivity measurements of sodium carbonate solutions at 25°. From the corrected figures, the mobility of the carbonate ion is found to be 69·3 ± 0·3.

THE extensive hydrolysis which occurs in sodium carbonate solutions causes the conductivity to be considerably greater than would be the case with the unhydrolysed salt. This is due to the

large proportion of sodium hydroxide present, and to the high mobility of the hydroxyl ion. The figures given hitherto have not been corrected for this effect (Int. Crit. Tables, VI, 249; Landolt–Börnstein, 5th edtn., 3rd supplement, p. 1073). In the measurements reported below, the extent of the hydrolysis has been calculated, and corresponding corrections made to the conductivity figures. The results have been used to deduce a conductivity curve for unhydrolysed sodium carbonate solutions.

The conductivity measurements were made on solutions formed by addition of a stock solution from a weight pipette fitted with a soda-lime guard to conductivity water which was kept under carbon dioxide-free air. The small amount of carbon dioxide present in conductivity water was calculated from its specific conductivity (Davies, " Conductivity of Solutions ", Chap. IV). This is necessary since the presence of carbon dioxide slightly modifies the main hydrolysis. The equivalent concentration range taken was from $C = 0{\cdot}001$ to $C = 0{\cdot}02$; the densities of these solutions were calculated from the relation $d_4^{25°} = 0{\cdot}99707 + 0{\cdot}054C$, which is based on available data (Int. Crit. Tables, III, p. 82). All resistance readings showed a slight drift with time, and this was allowed for as far as possible by taking time measurements and extrapolating back to the time of addition of the stock solution. This drift was no doubt due to the adsorption of hydroxyl ions by the cell walls. Similar effects with alkaline solutions have been noted by others (Darken and Meier, *J. Amer. Chem. Soc.*, 1942, **64**, 621). Because of this trouble it was not possible to study more dilute solutions.

In order to compute the concentrations of the various ions present, the equilibria to be taken into consideration are $CO_3'' + H_2O \rightleftharpoons HCO_3' + OH'$, and $OH' + CO_2 \rightleftharpoons HCO_3'$. The first of these alone would be the only one to consider if pure water had been used, and in this case $HCO_3' = OH'$. The second process goes almost to completion. This follows from the relation $K_w/K_1 = \{OH'\}\{CO_2\}/\{HCO_3'\}$, where $K_w = 1{\cdot}008 \times 10^{-14}$ (Harned and Hamer, *J. Amer. Chem. Soc.*, 1933, **55**, 2194) and K_1 (the first dissociation constant of carbonic acid) $= 4{\cdot}45 \times 10^{-7}$ (Harned and Davis, *ibid.*, 1943, **65**, 2030). Since the bicarbonate and hydroxyl ions are in almost identical concentrations, it follows that the concentration of carbon dioxide is negligibly small, being about $2{\cdot}5 \times 10^{-6}$. Accordingly, all the carbon dioxide is converted into bicarbonate. If m is the stoicheiometric molarity of the carbonate, x is the concentration of carbonate which hydrolyses, and y is the concentration of carbon dioxide present in the water before the addition of the salt, then it follows that the bicarbonate concentration is given by $HCO_3' = x + y$, and the concentration of hydroxide is given by $OH' = x - y$. The actual concentrations may therefore be deduced from the relation

$$\frac{K_w}{K_2} = K_h = \frac{\{OH'\}\{HCO_3'\}}{\{CO_3''\}} = \frac{(x-y)(x+y)f_1^2}{(m-x)f_2}$$

K_2, the second dissociation constant of carbonic acid, is $4{\cdot}69 \times 10^{-11}$ (Harned and Scholes, *ibid.*, 1941, **63**, 1706). The ion-activity coefficients f_1 and f_2 are for uni- and bi-valent ions, respectively. These were calculated from Davies's activity expression (*J.*, 1938, 2093). An approximation method was used in calculating the various ion concentrations. The resulting values of x, y, and the total ionic strength I are give in the table.

To obtain the corrected conductivity figures, a mixture rule was used :

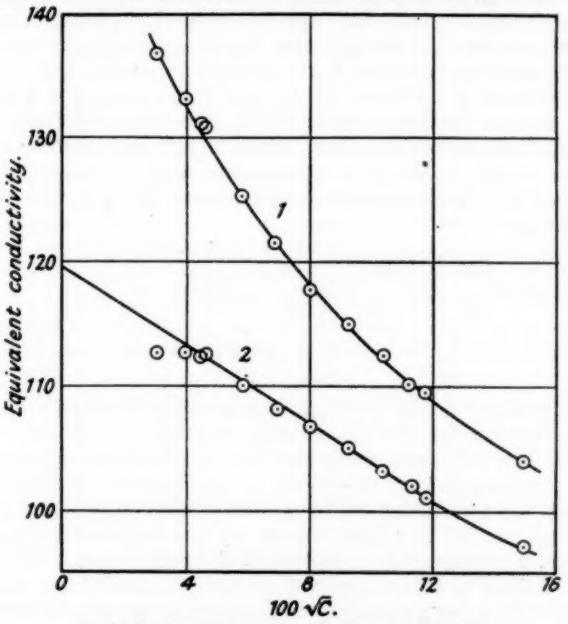
$$\Lambda_{(obs.)} = \Lambda_{(corr.)}(m - x) + \tfrac{1}{2}\Lambda_{NaOH}(x - y) + \tfrac{1}{2}\Lambda_{NaHCO_3}(x + y)$$

The conductivity of sodium hydroxide was taken from the data of Darken and Meier (*loc. cit.*), and that of sodium hydrogen carbonate was derived from that for potassium hydrogen carbonate (Shedlovsky and MacInnes, *J. Amer. Chem. Soc.*, 1935, **57**, 1705) and for sodium and potassium chlorides (Shedlovsky, *ibid.*, 1932, **54**, 1411). These give, for sodium hydrogen carbonate,

Run.	10^6y.	10^6C.	10^6x.	10^5I.	$\Lambda_{(obs.)}$.	$\Lambda_{(corr.)}$.
1	2·0	1130·8	249·6	144·7	136·7	112·5
2	4·9	1642·8	314·0	215·0	133·1	112·5
3	2·9	2061·3	358·9	273·8	131·1	112·3
4	2·5	2169·2	369·8	288·5	130·7	112·5
3	2·9	3503·0	484·9	477·0	125·3	110·3
5	4·2	4937·6	583·2	682·3	121·5	108·7
2	4·9	6562·1	676·5	916·7	118·2	106·9
5	4·2	8624·1	779·5	1216	115·1	105·1
5	4·2	10865	875·6	1542	112·5	103·2
6	6·2	12850	950·6	1835	110·5	101·9
2	4·9	13940	989·9	1992	109·6	101·4
6	6·2	22437	1243	3241	103·9	97·3

$\Lambda = 94{\cdot}58 - 81{\cdot}6C^{\frac{1}{2}}$. Since the solutions contained ions of mixed valencies, ionic strengths were used instead of concentrations in calculating the conductivities of the sodium hydroxide and the sodium hydrogen carbonate. The corrected conductivities for sodium carbonate are shown in the table. Extrapolation of the corrected conductivity figures leads to a Λ_0 value

Equivalent conductivity of sodium carbonate solutions at 25°.



1, *Experimental curve.* 2, *Corrected curve.*

of $119{\cdot}4 \pm 0{\cdot}3$, so, with allowance of 50·1 for the mobility of the sodium ion (Shedlovsky, *loc. cit.*), the mobility of the carbonate ion is $69{\cdot}3 \pm 0{\cdot}3$. Up to $C = 0{\cdot}005$, the corrected curve shown in the figure, where Λ is plotted against $C^{\frac{1}{2}}$, is represented by $\Lambda = 119{\cdot}4 - 152C^{\frac{1}{2}}$. The limiting Onsager equation is $\Lambda = 119{\cdot}4 - 174C^{\frac{1}{2}}$. These two equations are thus sufficiently close to indicate that the corrections are of the right order.

Experimental.

"AnalaR" Sodium hydrogen carbonate was heated at 265° in a platinum dish, and the resulting carbonate dissolved in conductivity water. The hydrogen carbonate was reprecipitated by carefully washed carbon dioxide, filtered off, and heated at 265° till it reached constant weight (Kolthoff and Sandell, "Textbook of Quantitative Inorganic Analysis", p. 547). The conductivity apparatus has been described previously (this vol., p. 422).

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[*Received, May 21st,* 1948.]

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98. *The Organic Derivatives of Gold. Part X. Diethylgold Cyclic Derivatives containing the* N–C–C–S *System.*

By (the late) R. V. G. Ewens and C. S. Gibson.

Diethylmonobromogold reacts quantitatively with 2-aminoethanethiol to give the non-electrolyte (*2-aminoethylthio*)*diethylgold* (I), in which the sulphur atom displays the reactivity typical of an organic sulphide. This compound yields a *sulphilimine* (VIII) and alkylates to yield a sulphonium cation, isolated as the *picrate* (as V). The constitution of the non-crystalline bromide is shown to be similar.

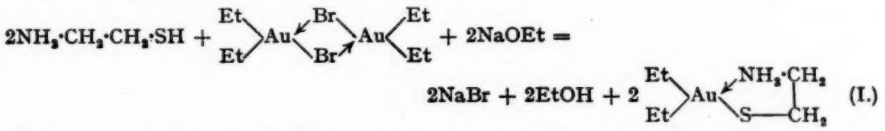
The stable (*dithio-oxamido*)*tetraethyldigold* (X), which contains a heterocyclic system similar to (I), has also been prepared.

The well-known affinity of the transitional metals for nitrogen and sulphur, as in the complexes with amines and sulphides, suggested that suitable aminothiols ought to form chelate complexes

of considerable stability. The simplest monoacidic chelating compound of this class, 2-aminoethanethiol, does not appear to have been investigated from this point of view, though a few complexes of cysteine—the carboxylated analogue—have been described (for the cobalt–cysteine complexes, see Schubert, *J. Amer. Chem. Soc.*, 1933, **55**, 3336).

Among the metals, nickel, palladium, copper, and particularly cobalt form well-defined complexes with 2-aminoethanethiol which will be described later. The dialkylgold derivative, however, is unique in containing only one organic residue and thus a single chelate ring. This characteristic feature (which is a normal one for the dialkylgold derivatives of bidentate compounds), arises because the univalent R_2Au group requires two further covalencies to satisfy the electronic requirements of the gold atom, and these links are disposed at an angle of approximately 90°. Simple univalent cations with a co-ordination number of two (*e.g.*, Ag^+, Cu^+) on the other hand have a normal valency angle of 180° and are thus not particularly suited to ring formation with a single molecule of a mono-chelating compound.

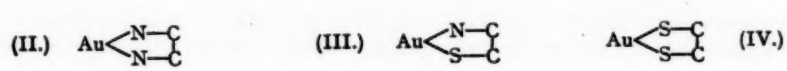
2-Aminoethanethiol and diethylmonobromogold react in the presence of sodium ethoxide according to the equation:



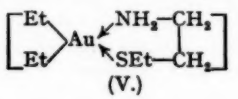
The change proceeds so rapidly that the hydrobromic acid liberated by the interaction of the thiol and diethylmonobromogold may be titrated with the sodium ethoxide, phenolphthalein being used as indicator. If the reaction is carried out in chloroform–ethanol the sodium bromide is precipitated and (2-*aminoethylthio*)*diethylgold* (I) can readily be isolated from the filtrate. The colourless crystals are unaffected by light over a long period, and this unusual stability among organic gold compounds is further shown by the high melting point (172—173°), the highest yet recorded for a mononuclear non-electrolyte in this series. The compound (I) is very soluble in chloroform, soluble in ethanol and other organic solvents mentioned below, but almost insoluble in acetone and ether; surprisingly it is, however, somewhat soluble in hot water.

The difficulty in establishing the molecular weight of the compound in solution affords a curious contrast when set against the stability in the solid state. In benzene, in which the complex is but sparingly soluble, the value first obtained indicates that the substance is monomeric (*M*, found: approx. 300. Calc.: 331), but the freezing-point depression rapidly decreases and oily material accumulates on the walls of the vessel. The change is probably due to oxidation, and the use of an inert atmosphere would have determined this; but because of the limited solubility the attainable depressions are in any case so low that a change of solvent appeared to be a more advantageous step; experiments in benzene were therefore abandoned. In pure bromoform the reactivity is obvious; the solution rapidly becomes turbid through the separation of a colourless amorphous product. This behaviour is not surprising in view of the reaction of the compound with alkyl halides (see below), but it makes even the initial freezing-point depressions unreliable and the apparent molecular weights are in fact always high (*e.g.*, 438, 443), but lie between the values for the monomeric and the dimeric formula. In nitrobenzene, in which the solubility is again limited, the immediate production of a bright yellow colour clearly indicates the formation of a molecular compound, and recalls the well-known behaviour of polynitro-compounds, such as tetranitromethane, with unsaturated substances. The complex (I) is readily recovered unchanged from the nitrobenzene solution by precipitation with ether. The apparent molecular weight in nitrobenzene (363) is little more than that of the monomer. In a fourth solvent, glacial acetic acid, the behaviour appears to be normal (*M* 322), but the complex is nevertheless slowly decomposed by the acid and on standing the solution deposits a colourless amorphous substance. While none of these results alone is thus completely satisfactory, the weight of evidence in favour of the monomeric formula is cumulatively strong.

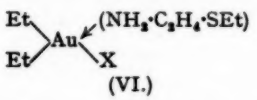
The instability in solution may be due partly to ring strain, because heterocyclic systems containing one or more relatively large atoms must necessarily be distorted. The ring type (II) is familiar in ethylenediaminediethylgold bromide (Et_2Au en)Br. We have obtained evidence (unpublished) that the ring system (IV) is unstable; hence the ring system (III) is obviously strained.



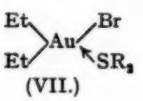
The sulphur atom in (2-aminoethylthio)diethylgold shows a reactivity akin to that of organic sulphides. The solid complex reacts vigorously with methyl iodide—explosively on a 0·5 g. scale—while in solution the methylation proceeds so rapidly and so far that no definite compound can be isolated. With ethyl bromide in ethanol the reaction proceeds much more smoothly, but the syrup obtained on evaporation cannot be induced to crystallise. Nevertheless we show (i) that alkylation takes place at the sulphur atom and (ii) that the product is essentially the salt (V) rather than a compound having the alternative covalent structure (VI), where X = Br. Our proof is as follows. When diethylmonobromogold is treated with ethyl 2-aminoethyl



(V.)



(VI.)



(VII.)

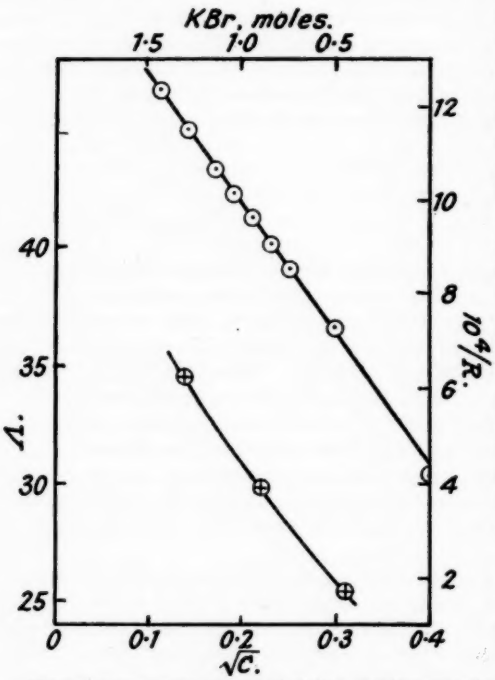
sulphide, $NH_2{\cdot}CH_2{\cdot}CH_2{\cdot}SEt$, an oil resembling that obtained by direct alkylation of the complex (I) is produced. Both are freely soluble in most organic solvents other than hydrocarbons, and also to some extent in water. Since our inability to obtain a crystalline bromide by either route might have been due to the presence of an equilibrium mixture of (V) and (VI), especially if (VI) had a low enough melting point (cf. the acetylacetonate of m. p. 10°; Gibson and Simonsen, *J.*, 1930, 2531), it was clearly desirable to introduce an alternative anion of lower co-ordinating power so that the salt form (V) would be favoured. Treatment of an ethanolic solution containing diethylmonobromogold and ethyl 2-aminoethyl sulphide with silver nitrate or perchlorate readily eliminates the halogen, but the resulting salts are too soluble and deliquescent to be suitable for further study. The ion in (V) should be resolvable because of the asymmetry at the sulphur atom; but the (+)-α-bromocamphor-π-sulphonate, prepared in the same way, showed no sign of crystallisation.

Sodium picrate on the other hand precipitates (*ethyl 2-aminoethyl sulphide*)*diethylgold picrate* from the aqueous-alcoholic solution, and the new compound crystallises readily in the form of large lemon-yellow lustrous and transparent prisms. The picrate is definitely a salt and conducts well in ethanol. For a 0·0193M-solution at 25·5°, Λ is 34·5 ohms^{-1} (compare Λ = 32·35 for 0·01M-tetraethylammonium picrate in ethanol at 25°; Walden, Ulich, and Laun, *Z. physikal. Chem.*, 1925, **114**, 275) (see also the Figure). Further, the oil obtained by the action of ethyl bromide on the parent complex (I) yields in similar fashion a picrate of identical crystalline form, having the same m. p. and mixed m. p.; hence the alkylation must have taken place on the sulphur atom. The picrate, like compound (I), is stable to light. It is slightly soluble in water, moderately so in chloroform, and readily in ethanol.

The hypothesis that the uncrystallisable bromide might be partly or wholly the covalent compound (VI) is superficially attractive. It is well known that the halides in general are better co-ordinating groups than less polarisable oxy-anions, and it was observed by Weitz (*Annalen*, 1915, **410**, 117) that *tetra*ammines of tervalent gold $[Au(NH_3)_4]X_3$ could readily be made when X = NO_3, ClO_4, etc., but not when X is a halide ion. It may be remarked that in the dialkylgold series the stability of the M–X link appears to increase with the atomic number (and polarisability) of the halogen; for instance, dimethyl*iodo*gold is formed when methylmagnesium iodide acts on pyridinetri*chloro*gold (Brain and Gibson, *J.*, 1939, 762). The same order is frequently observed in the complexes of the more noble metals, though it is by no means universal and is frequently upset by oxidation–reduction phenomena or for steric reasons. The commonest cases of co-ordination through sulphur occur with thiourea and with alkyl sulphides, of which only the latter concern us here. Brain and Gibson (*loc. cit.*) observed that only one molecule of dibenzyl sulphide could be introduced into diethylmonobromogold as in (VII; R = CH_2Ph), whence we infer that the Br^- ion co-ordinates more strongly than the sulphide. (The complex derived from the more volatile diethyl sulphide is even less stable.) Finally, these authors prepared a complex analogous to (V) using *as*-*N*-diethylethylenediamine (*i.e.*, with NEt_2 in place of SEt) and isolated it as the bromide, though here the crystallisation offered some difficulty. In water the compound behaved as a salt, the molecular weight indicating the presence of two ions. Since the solubility in organic solvents was appreciable, the conversion into the covalent form analogous to (VI) was proposed under these conditions, and to explain the observed polymerisation in bromoform a structure involving 5-covalent gold was postulated.

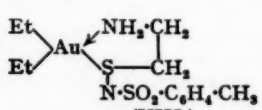
All these arguments may be adduced in favour of the possible existence of structure (VI). On the other hand, if the covalent form of (ethyl 2-aminoethyl sulphide)diethylgold bromide were of any importance in aqueous-alcoholic solution, then on adding potassium bromide the

conductivity of a picrate solution should not increase steadily but should show some sort of inflexion of the type commonly observed in conductometric analysis, owing to the formation of some covalent complex. As indicated in the figure, however, no such effect is observed. It must therefore be concluded that the co-ordination of the sulphur is *stronger* than that of the bromide ion, notwithstanding the possible ring strain, because of the stabilising effect of the chelate ring. The stability constants of a number of ammonia and ethylenediamine complexes determined by Bjerrum ("Complex Ammine Formation in Aqueous Solution", Copenhagen, 1941) afford numerous examples of this effect. Further, it is not necessary to assume a covalent form to explain the solubility of such complexes in organic solvents since many alkylammonium halides with considerable hydrocarbon content, and of undoubted salt-like character, behave thus. Moreover, the solutes display multiple ion association at all but the lowest concentrations, and Brain and Gibson's molecular-weight observations on the unsymmetrical diamine complex are no doubt explicable in this way.

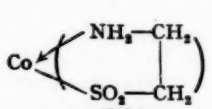


Upper curve, axes top and right: conductometric titration of complex picrate with potassium bromide. Lower curve, axes left and bottom: conductivity of complex picrate in ethanol at 25·5°.

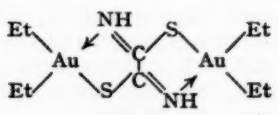
Among other properties of 2-aminoethylthiodiethylgold characteristic of an organic sulphide is its behaviour with chloramine-T, which reacts to give the crystalline sulphilimine (VIII). Qualitatively, it was found that (I) decolourised halogen solutions, yielded amorphous and unstable precipitates with the mercuric halides, and underwent oxidation easily. No "sulphoxide" or "sulphone" could be isolated, however, though the complex of tervalent cobalt with the aminothiol does yield the corresponding M–SO_2– compound (IX) (Ewens, unpublished result).



(VIII.)

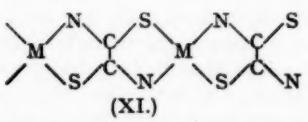


(IX.)

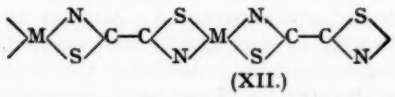


(X.)

Lastly, to furnish additional evidence for the ring system (III), we prepared the diethylgold derivative of dithio-oxamide (rubeanic acid) by its interaction with diethylmonobromogold in the presence of alkali. *(Dithio-oxamido)tetraethyldigold* (X) forms yellow prisms from benzene or chloroform and has a molecular weight in benzene in agreement with the formula assigned to it. No doubt the ring system here is stabilised by the single–double bond resonance in the thiocarbamido-groups. Certainly this compound showed none of the reactivity associated with (I).



(XI.)



(XII.)

Structure (X), which resembles that for the corresponding oxalate complex (Gibson and Weller, *J.*, 1941, 102), is a model for the analytically well-known precipitates given by rubeanic acid with the bivalent nickel, copper, and cobalt ions; a co-ordination number of four requires infinite polymerisation as in (XI) and this formulation, with five-membered rings, is preferable to that of Jensen (*Z. anorg. Chem.*, 1944, **252**, 227), who proposed the alternative arrangement (XII) with four-membered rings.

Experimental.

(2-*Aminoethylthio*)*diethylgold.*—To diethylmonobromogold (6·7 g., 1 mol.) and freshly sublimed 2-aminoethanethiol (1·5 g., 1 mol.) in chloroform (80 ml.) was added 0·651M-sodium ethoxide (1 mol.). The solution was filtered from the precipitated sodium bromide, evaporated, and the residue recrystallised from ethanol to yield 5·76 g. (87%) of colourless needles of (2-*aminoethylthio*)*diethylgold*, m. p. 172—173° (decomp.) (Found: C, 21·9; H, 4·4; N, 4·5; Au, 59·4. $C_6H_{16}NSAu$ requires C, 21·7; H, 4·9; N, 4·2; Au, 59·5%). Molecular weight determinations (the concentrations C given are in g. of solute/1000 g. of solvent): (a) *In benzene.* $C = 3·62$, $\Delta t = 0·062°$, $M = 298$. ($C_6H_{16}NSAu$ requires M, 331.) The depression rapidly decreased to *ca.* 0·02° with obvious signs of decomposition. Initial depressions for solutions of higher concentration could not be determined because of the low solubility. (b) *In bromoform.* The results in this solvent were affected by reaction and the formation of an insoluble product. Two typical results are (i) $C = 2·25$, $\Delta t = 0·074°$, $M = 438$; (ii) $C = 3·23$, $\Delta t = 0·105°$, $M = 443$. (c) *In nitrobenzene.* The compound formed a bright yellow solution. For $C = 12·64$, $\Delta t = 0·240°$ (unchanged by the addition of anhydrous sodium sulphate; compare Roberts and Bury, *J.*, 1923, 2037), whence $M = 363$. On increase of the concentration to $C = 19·78$, Δt rose to 0·347°, but was unchanged on the addition of further solute so that this solution presumably became saturated on cooling. Almost pure compound was recovered by precipitation with ether. (d) *In glacial acetic acid.* $C = 9·09$, $\Delta t = 0·110°$, $M = 322$. A steady decomposition set in and the solution deposited a colourless insoluble decomposition product which was not further examined.

(2-*Aminoethylthio*)*diethylgold sulphilimine.* To (2-aminoethylthio)diethylgold (0·5 g., 1 mol.) in ethanol (5 ml.) was added slowly chloramine-T (0·37 g.: 1·08 mols.) in water (7·5 ml.). The colourless *sulphilimine* rapidly separated, and after being washed with water was recrystallised from ethanol to form granular clusters of needles (0·53 g., 71%), m. p. 136° (decomp.) (Found: C, 30·7; H, 4·6; N, 5·7; Au, 39·3. $C_{12}H_{32}O_2N_2S_2Au$ requires C, 31·2; H, 4·6; N, 5·6; Au, 39·4%). The sulphilimine was readily soluble in chloroform, slightly in benzene, and slowly decomposed on keeping.

(*Ethyl 2-aminoethyl sulphide*)*diethylgold picrate.* (a) To finely divided diethylmonobromogold (3·35 g., 1 mol.) suspended in water were added ethyl 2-aminoethyl sulphide (1·05 g., 1 mol.) and then aqueous silver nitrate (1·70 g., 1 mol.) to make the total volume *ca.* 50 ml. Silver bromide immediately began to separate and, after a few hours' shaking to ensure complete reaction, was filtered off. (The filtrate contained the complex nitrate, which crystallised with great difficulty and was very soluble and deliquescent. The perchlorate and (+)-α-bromocamphor-π-sulphonate, produced similarly in water or other solvent, also crystallised poorly.) A slight excess of sodium picrate solution was added and precipitated (*ethyl 2-aminoethyl sulphide*)*diethylgold picrate.* A more convenient procedure, which avoided the elimination of the halogen, is as follows.

(b) Diethylmonobromogold (0·67 g., 1 mol.) and ethyl 2-aminoethyl sulphide (0·2 g., 1 mol.) were dissolved in ethanol (10 ml.)—from which the complex bromide could only be obtained as a syrup—and the solution diluted with an equal volume of water. Sodium picrate (0·55 g., 1·2 mols., in 15 ml.) gave a yellow crystalline precipitate, which was filtered off, washed with water, and recrystallised from aqueous ethanol to yield 0·87 g. (74%) of large lustrous yellow prisms; m. p. 120—121°, followed by rapid decomposition and gas evolution at *ca.* 134° (Found: C, 29·05; H, 4·4; N, 9·8; Au, 33·15. $C_{14}H_{22}O_7N_4SAu$ requires C, 28·6; H, 3·9; N, 9·5; Au, 33·5%). The compound was very slightly soluble in water, moderately so in chloroform. The conductivity in ethanol at 25·5°, measured in the usual manner, gave the following results. Concentration 0·0964M, $\Lambda = 25·4$; 0·0482M, $\Lambda = 29·8$; 0·0193M, $\Lambda = 34·5$ ohms^{-1}.

Conductometric titration. For reasons already given, the effect of bromide ion on the conductivity was examined. To 25 ml. of a 0·00817M-solution of the picrate in 75% v/v aqueous ethanol at 25° was added in small portions 0·1009M-potassium bromide in the same solvent. The variation of the reciprocal resistance (plotted in the figure) was linear, and showed no sign of any inflexion which would have indicated the formation of a covalent complex.

Action of alkyl halides. Under a variety of conditions methyl iodide reacted to give mixtures of colourless and yellow products which could not be satisfactorily separated, of high iodide content. Ethyl bromide similarly furnished mixtures, mostly of a syrupy nature, as in the following experiment. A solution of (2-aminoethylthio)diethylgold (0·335 g.) and ethyl bromide (0·2 ml.) in ethanol (5 ml.) was allowed to stand overnight and then evaporated. The gummy residue, which contained a few ill-defined crystals but showed no signs over a long period of crystallising further, was redissolved in ethanol, and addition of an excess of aqueous sodium picrate gave a precipitate which, treated as before, furnished 0·14 g. of a picrate identical in crystalline form, melting point, and mixed melting point with the authentic product above.

(*Dithio-oxamido*)*tetraethyldigold.*—To a solution of diethylmonobromogold (2·24 g.) in ligroin (b. p. 40—60°; 20 ml.) was added a warm solution of dithio-oxamide (0·4 g., 1 mol. to 2 Au) and the calculated amount of potassium hydroxide (2 mols.) in ethanol (40 ml.). Potassium bromide was immediately precipitated and filtered off. The filtrate was evaporated down and the residue extracted with chloroform. On addition of ligroin (b. p. 60—80°), (*dithio-oxamido*)*tetraethyldigold* (1·62 g., 77%) crystallised in yellow prisms, m. p. 142—143° (decomp.) (Found: Au, 62·5. $C_{10}H_{22}N_2S_2Au_2$ requires Au, 62·5%). Molecular weight in benzene: $C = 8·65$, $\Delta t = 0·069°$, $M = 636$; $C = 19·44$, $\Delta t = 0·154°$, $M = 640$ ($C_{10}H_{22}N_2S_2Au_2$ requires M, 628).

We wish to thank Messrs. Imperial Chemical Industries Ltd. for financial aid, and also Dr. W. E. Jones for supplying the 2-aminoethanethiol and the ethyl 2-aminoethyl sulphide.

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[*Received, May 19th*, 1948.]

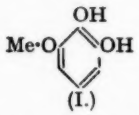
99. *The Synthesis of Myristicin.*

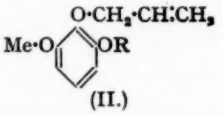
By V. M. Trikojus and D. E. White.

The allylation of pyrogallol 1-methyl ether (I) and the synthesis of myristicin from the *pyrogallol* 1-*methyl* 2-*allyl ether* (II; R = H) so formed, are described. The higher-boiling *pyrogallol* 1-*methyl* 3-*allyl ether* (III; R = H) also yields myristicin, apparently by migration of the allyl group to the meta-position.

Myristicin is the major constituent of the higher-boiling fractions of nutmeg and mace oils, and it was shown by Thoms (*Ber.*, 1903, **36**, 3446) to be 1-methoxy-2 : 3-methylenedioxy-5-allylbenzene (V). This structure was confirmed by the synthesis of myristicinaldehyde (Baker, Montgomery, and Smith, *J.*, 1932, 1281), and is now further confirmed by the synthesis of myristicin itself, a preliminary report of which was given in a letter to *Nature* (1939, **144**, 1016).

Allylation of pyrogallol 1-methyl ether (I) (Baker and Savage, *J.*, 1938, 1602) gave two monoallyl ethers differing in boiling point by 5°. The lower-boiling ether was characterised by its 3 : 5-*dinitrobenzoate* and identified as *pyrogallol* 1-*methyl* 2-*allyl ether* (II; R = H) by methylation to the 1 : 3-dimethyl ether (II; R = Me) (Mauthner, *Annalen*, 1917, **414**, 250; Hahn and Wassmuth, *Ber.*, 1934, **67**, 696) which was characterised by rearrangement to 2-hydroxy-1 : 3-dimethoxy-5-allylbenzene (IV; R = H, R′ = Me), identified as its 3 : 5-*dinitrobenzoate*.


(I.)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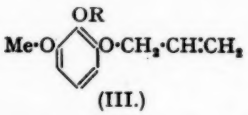
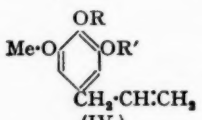

(III.)

Pyrolysis of (II; R = H) gave 2 : 3-*dihydroxy*-1-*methoxy*-5-*allylbenzene* (IV; R = R′ = H), which formed a crystalline *monoacetate* and *diacetate*, and on treatment with methylene iodide and potassium carbonate, by the method of Perkin and Trikojus (*J.*, 1927, 1663), was converted into myristicin (V), identical with the natural product obtained from oil of nutmeg. This identity was established by the comparison of samples of tetrabromomyristicin, *iso*myristicin, and tetrabromo*iso*myristicin prepared from natural and synthetic myristicin.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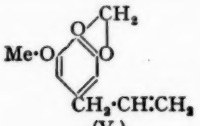
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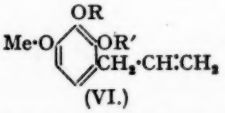
(VI.)

The higher-boiling monoallyl ether was identified as *pyrogallol* 1-*methyl* 3-*allyl ether* (III; R = H) since on methylation and pyrolysis it yielded the same *phenol* (3 : 5-*dinitrobenzoate*) as did pyrolysis of authentic 1 : 2-dimethoxy-3-allyloxybenzene (III; R = Me), prepared from pyrogallol 1 : 2-dimethyl ether (Baker and Smith, *J.*, 1931, 2542; cf. Baker and Savage, *J.*, 1938, 1602). On pyrolysis of (III; R = H) and methylenation of the product, myristicin was again obtained, although in somewhat smaller yield than before. Methylation of the product of pyrolysis of (III; R = H) gave 3 : 4 : 5-trimethoxy-1-allylbenzene (IV; R = R′ = Me), identified by conversion into 3 : 4 : 5-trimethoxybenzoic acid (*O*-trimethylgallic acid). Thus it appears that the allyl group has migrated to the meta-position in this pyrolysis. Pyrolysis of the methyl and ethyl ethers of (III; R = H), however, showed the normal migration of the allyl group to the ortho-position, yielding (VI; R = Me, R′ = H) and (VI; R = Et, R′ = H) respectively.

Migration of the allyl group to the meta-position may be largely influenced by the 2-hydroxyl group and may explain the formation of 1 : 2-dihydroxy-3 : 4-dimethoxy-5-allylbenzene exclusively in the pyrolysis of the crude monoallyl ether of 1 : 2-dihydroxy-3 : 4-dimethoxybenzene (Baker, Jukes, and Subrahmanyam, *J.*, 1934, 1681).

Experimental.

Allylation of Pyrogallol 1-*Methyl Ether.*—Finely powdered, anhydrous potassium carbonate (18 g.) was suspended in acetone (20 ml.) in an atmosphere of hydrogen, and a solution of crystalline pyrogallol 1-methyl ether (Baker and Savage, *loc. cit.*; cf. Surrey, *Org. Synth.*, 1946, **26**, 90; 18 g.) dissolved in acetone (40 ml.) slowly added. The potassium salt of the phenol crystallised and set to a solid mass but this gradually disintegrated on adding allyl bromide (16 g.) and boiling under reflux for 5 hours. After

distillation of the acetone and dissolution of the solids in 2N-sulphuric acid (100 ml.), the crude product was extracted twice with ether, and the phenols isolated by extraction of the ethereal solution with sodium hydroxide (8 g. in all) in water (100 ml.). The alkaline solution was immediately acidified with hydrochloric acid, and the liberated phenols removed by two extractions with chloroform. Unchanged pyrogallol 1-methyl ether was removed from the chloroform solution by shaking it with lead acetate solution (twice) until no more lead salt was precipitated. After removal of the lead salt by filtration, the chloroform solution was dried (Na_2SO_4), the chloroform evaporated, and some residual inorganic material removed by extraction with light petroleum (b. p. 40—60°) and filtration of the solution. On removal of the petroleum the mixed monoallyl ethers (13·5 g.) distilled at 0·3—0·35 mm./130° (bath temp.), as a colourless oil. Distillation through a 10 cm. Widmer column gave two fractions: *A*, b. p. 98°/0·45—0·42 mm., and *B*, b. p. 103—106°/0·55—0·52 mm. These were refractionated with the same column, fraction *B* being added to the distillation flask after the first two fractions had been collected. The fractions obtained were as follows:

1. B. p. 92·5—94°/0·25 mm. (4 g.) (Found: C, 66·2; H, 6·7. $C_{10}H_{12}O_3$ requires C, 66·6; H, 6·7%), identified below as *pyrogallol 1-methyl 2-allyl ether*. 50 Mg. heated for 1 hour with 3 : 5-dinitrobenzoyl chloride (70 mg.) and pyridine (0·5 ml.) on the water-bath, kept at room temperature overnight, and then heated for a further 45 minutes, gave the 3 : 5-*dinitrobenzoate* as a pale yellow solid after being treated with dilute hydrochloric acid and washed with sodium carbonate solution and water. It formed colourless needles from 90% alcohol, m. p. 111—112° (Found: N, 7·7. $C_{17}H_{14}O_8N_2$ requires N, 7·48%).
2. B. p. 93—95°/0·25 mm. (1·6 g.).
3. B. p. 97·5—100°/0·25 mm. (2·1 g.).
4. B. p. 99—104°/0·2 mm. (4·4 g.) (Found: C, 66·7; H, 6·75. $C_{10}H_{12}O_3$ requires C, 66·6; H, 6·7%), identified below as *pyrogallol 1-methyl 3-allyl ether*. Its 3 : 5-*dinitrobenzoate*, prepared as with the isomer above, crystallised as pale straw-coloured needles from alcohol, m. p. 133—134° (Found: N, 7·58. $C_{17}H_{14}O_8N_2$ requires N, 7·48%).*

Identification of Fraction 1.—Fraction 1 (0·8 g.) was methylated with methyl sulphate and 10% potassium hydroxide solution, the product extracted with ether, and the extract washed with dilute potassium hydroxide solution and with water and then dried and distilled in a vacuum, yielding a pale yellow oil (0·8 g.), which was heated in an oil-bath till the temperature of the liquid rose above the temperature of the bath (at 225°), heating being continued until the temperatures became equal again. On cooling, the product was dissolved in sodium hydroxide solution, and the solution washed with ether, acidified, and extracted with ether. After drying and removal of the ether, the residual yellow oil was converted into its 3 : 5-*dinitrobenzoate*, which formed canary-yellow aggregates of needles from alcohol, m. p. 129—130° (Found: N, 7·34. $C_{18}H_{16}O_8N_2$ requires N, 7·21%).

Authentic pyrogallol 1 : 3-dimethyl 2-allyl ether was prepared by the method of Mauthner (*loc. cit.*; cf. Hahn and Wassmuth, *loc. cit.*) and rearranged to 2-hydroxy-1 : 3-dimethoxy-5-allylbenzene, the 3 : 5-dinitrobenzoate of which formed identical canary-yellow aggregates from alcohol, m. p. 129—130°, alone or mixed with the ester described above (Found: N, 7·35%).

2 : 3-*Dihydroxy*-1-*methoxy*-5-*allylbenzene* (IV; R = R′ = H).—Pyrogallol 1-methyl 2-allyl ether (Fraction 1; 2 g.) was heated in an atmosphere of hydrogen to 170—175°; the temperature of the liquid rose rapidly to 237°, then fell, and was kept by external heating at 200° for 1 minute. On distillation, 2 : 3-*dihydroxy*-1-*methoxy*-5-*allylbenzene* was obtained as a viscous oil, b. p. 112·5—115°/0·22—0·3 mm. (1·9 g.) (Found: C, 66·0; H, 6·9. $C_{10}H_{12}O_3$ requires C, 66·6; H, 6·7%), which on treatment with acetic anhydride and pyridine at room temperature for 24 hours, followed by washing with water and sodium hydrogen carbonate solution gave a *monoacetate*, colourless needles, m. p. 98—99°, on crystallisation from dilute alcohol and then from ether–light petroleum (Found: C, 64·8; H, 6·8. $C_{12}H_{14}O_4$ requires C, 64·9; H, 6·35%). Acetylation of the 2 : 3-dihydroxy-1-methoxy-5-allylbenzene (0·3 g.) with acetic anhydride (1·25 ml.) and pyridine (1 ml.) at 100° for 1 hour, followed by standing overnight at room temperature, treatment with 2N-sulphuric acid and ether, and washing the ether solution with 2N-sulphuric acid and 2N-sodium carbonate, and drying, gave, on evaporation of the ether and treatment with light petroleum (b. p. 60—80°; 3 ml.), 2 : 3-*diacetoxy*-1-*methoxy*-5-*allylbenzene*, thick, colourless, pointed prisms from ether–light petroleum (b. p. 40—60°), m. p. 75—76° (Found: C, 63·6; H, 6·05. $C_{14}H_{16}O_5$ requires C, 63·6; H, 6·1%).

Myristicin (V).—2 : 3-Dihydroxy-1-methoxy-5-allylbenzene (2·9 g.) was dissolved in acetone (15 ml.), methylene iodide (4·3 g.) and potassium carbonate (2·2 g.) added, and the mixture refluxed on a boiling water-bath in an atmosphere of hydrogen. After 5 hours more potassium carbonate (2·2 g.) and methylene iodide (1·1 g.) were added, and refluxing continued for a further 2 hours. After removal of the acetone, ether and 2N-sulphuric acid (25 ml.) were added, and the ether solution was separated and washed with 2N-sodium hydroxide (20 ml. in all), dried, and distilled, yielding myristicin (1·03 g.), b. p. 95—97/0·2 mm., $n_D^{20°}$ 1·5426 (Found: C, 68·6; H, 6·01. Calc. for $C_{11}H_{12}O_3$: C, 68·7; H, 6·3%). This was characterised by treatment of 0·2 g. with bromine (0·3 ml.), added dropwise below 0°, the excess bromine being removed in a vacuum after a few minutes; the tetrabromo-derivative remained, and was washed with alcohol; it crystallised from alcohol as colourless needles (0·25 g.), m. p. 128° (Found: C, 26·1; H, 2·2; Br, 62·5, 62·7. Calc. for $C_{11}H_{10}O_3Br_4$: C, 25·9; H, 2·0; Br, 62·8%), identical with the tetrabromo-derivative obtained similarly from authentic myristicin, b. p. 148—151°/16 mm., $n_D^{20°}$ 1·5403, obtained by fractionation of oil of nutmeg.

iso*Myristicin*.—Synthetic myristicin (0·2 g.) was heated for 48 hours on the boiling water-bath with potassium hydroxide (powdered; 0·8 g.) and alcohol (3 ml.). On steam distillation the drops of oil obtained crystallised on cooling, and formed colourless needles from alcohol (50 mg.), m. p. 43°, alone

* *Added in Proof.*—Surrey's (*J. Amer. Chem. Soc.*, 1948, **70**, 2887) failure to separate or even to distil the monoallyl ethers of pyrogallol 1-methyl ether, without rearrangement, may be due to contamination of his material with pyrogallol 1-methyl ether or with oxidation products. When prepared and purified by the above method no difficulty was experienced in fractionating quantities up to 25 g. without rearrangement, although rearrangement was rapid at 170° (bath temp.).

or mixed with *iso*myristicin obtained by similar treatment of the natural product. *iso*Myristicin (natural or synthetic), on treatment with bromine as described for myristicin, gave the tetrabromo-derivative, m. p. 159°, separately or mixed.

Identification of Fraction 4 (III; R = H).—(a) *Methylation and pyrolysis.* Fraction 4 (1·9 g.) was treated with methyl sulphate (3 lots of 2 ml. each) and shaken, with addition of 10% sodium hydroxide solution till alkaline, after each lot of methyl sulphate. The methyl ether was then isolated by extraction with ether, the extract being washed with 10% sodium hydroxide and water, dried, and the ether evaporated. The residual oil was then rearranged by being heated to 235° for 15 minutes, during which time the temperature in the liquid rose to 3° below that of the bath temperature, then fell and remained steady 5° below the bath temperature. The product was distilled, b. p. 95—100°/0·12 mm. (1·0 g.), dissolved in ether, and extracted with 10% sodium hydroxide, the extract acidified, and the phenolic product again extracted with ether and again distilled. It was characterised by preparation of the 3 : 5-*dinitrobenzoate* by heating the oil (0·2 g.), 3 : 5-dinitrobenzoyl chloride (0·3 g.), and pyridine (1 ml.) for 1 hour at 100°. On cooling, adding 2N-sulphuric acid and ether, washing the ether solution with acid, water, 2N-sodium hydroxide and water again, drying, and evaporating the ether, the crude ester crystallised (0·14 g.), m. p. 115—116°, and formed pale yellow needles from alcohol, m. p. 118—119·5° (Found: N, 7·2. $C_{18}H_{16}O_8N_2$ requires N, 7·2%).

(b) *Pyrolysis of authentic pyrogallol* 1 : 2-*dimethyl* 3-*allyl ether.* The required *ether* (III; R = Me) was prepared by allylation of pyrogallol 1 : 2-dimethyl ether (Baker and Smith; Baker and Savage, *locc. cit.*) (4·1 g.) dissolved in acetone (25 ml.) with allyl bromide (3·5 ml.) and potassium carbonate (dry, sieved; 4·1 g.) by refluxing for 6 hours. The mixture was then diluted with water, the acetone distilled, and the product isolated by extraction with ether, the extract being washed with 10% sodium hydroxide and water, dried, the ether removed, and the residual oil distilled, b. p. 98—103°/0·2 mm. (3·8 g.) (Found: C, 68·0; H, 7·2. $C_{11}H_{14}O_3$ requires C, 68·1; H, 7·3%).

Pyrolysis of pyrogallol 1 : 2-dimethyl 3-allyl ether (2·1 g.) followed the same course as described above for the methyl ether of Fraction 4, except that more heat was evolved and the temperature of the liquid rose to 5° above the bath temperature. The pyrolysis product (oriented by the methods described below as 3-*hydroxy*-1 : 2-*dimethoxy*-4-*allylbenzene*) was distilled, b. p. 103—105°/0·25 mm. (Found: C, 67·9; H, 7·2. $C_{11}H_{14}O_3$ requires C, 68·1; H, 7·3%), and 0·2 g. converted into the 3 : 5-dinitrobenzoate as described above. The crude ester (0·16 g.), m. p. 116—117°, formed pale yellow needles from alcohol, m. p. 118—119·5°, alone or mixed with the material derived from Fraction 4 (Found: N, 7·2%).

(c) *Orientation of the* 3-*hydroxy*-1 : 2-*dimethoxy*-(x)-*allylbenzene.* (i) The 3-hydroxy-1 : 2-dimethoxy-(*x*)-allylbenzene obtained above (5 g.) was methylated with methyl sulphate (2 lots of 5 ml.) and 10% sodium hydroxide, the mixture being finally heated to 100° for 10 minutes and the methyl ether isolated by extraction with ether. The allyl group was then isomerised by treatment of the methyl ether (4·2 g.) with potassium hydroxide (15·6 g.) in alcohol (60 ml.) for 48 hours on the steam-bath, the product being isolated by steam distillation and extraction of the distillate with ether (3·5 g.), and then oxidised by adding potassium permanganate (powdered; 7 g.) gradually with shaking to the solution in acetone (140 ml.). Heat was evolved, and the reaction was completed by warming the mixture for a few minutes on the steam-bath. Excess of permanganate and manganese dioxide were then reduced by passing sulphur dioxide into the solution. The oxidation product separated and formed colourless needles from water (0·5 g.), m. p. 99—102°, undepressed by admixture with 2 : 3 : 4-trimethoxybenzoic acid of similar melting point.

(ii) The above 3-hydroxy-1 : 2-dimethoxy-(*x*)-allylbenzene (7·5 g.) was dissolved in 10% sodium hydroxide (300 ml.) and heated to the boiling point during the gradual addition of ethyl sulphate (32 ml.; 30 minutes). After 2 hours' refluxing the ethyl ether was isolated by extraction with ether, and the recovered phenol again treated, using the same procedure and combining the products. On distillation, the product was obtained as a pale yellow oil, b. p. 150—152/22 mm. (7·5 g.), identified below as chiefly 1 : 2-*dimethoxy*-3-*ethoxy*-4-*allylbenzene* (Found: C, 69·8; H, 8·0. $C_{13}H_{18}O_3$ requires C, 70·2; H, 8·1%).

The allyl group was isomerised by treatment of 6 g. with potassium hydroxide (26 g.) in alcohol (100 ml.) for 48 hours on the steam-bath, the propenyl compound being isolated by steam distillation and extraction of the distillate with ether. 1 : 2-*Dimethoxy*-3-*ethoxy*-4-*propenylbenzene* was obtained as a colourless oil, b. p. 163—167°/24 mm. (4·9 g.) (Found: C, 70·1; H, 8·3. $C_{13}H_{18}O_3$ requires C, 70·2; H, 8·1%).

The constitution of this product (4·0 g.) was shown by oxidation with potassium permanganate (8 g.) in acetone (160 ml.) as described above for the trimethoxy-compound. The acid oxidation product in this case separated as an oil which crystallised on cooling (1·5 g.) and was purified by crystallisation first from dilute alcohol (charcoal) and then thrice from dilute methyl alcohol; it formed colourless needles, m. p. 79—81°, identical with authentic 3 : 4-dimethoxy-2-ethoxybenzoic acid (Manske, Ledingham, and Holmes, *loc. cit.*) (Found: C, 58·5; H, 6·4. Calc. for $C_{11}H_{14}O_5$: C, 58·4; H, 6·2%).

Pyrolysis of Pyrogallol 1-*Methyl* 3-*Allyl Ether* (III; R = H).—Fraction 4 (4 g.) was heated in an atmosphere of hydrogen; rearrangement took place at *ca.* 190°, the temperature of the liquid rising above the bath temperature. After 15 minutes' heating the product was distilled as a colourless, viscous oil, b. p. 114—116°/0·2 mm. (3·5 g.) (Found: C, 66·6; H, 6·7. Calc. for $C_{10}H_{12}O_3$: C, 66·6; H, 6·7%).

Myristicin from the pyrolysis product. The above pyrolysis product (3·3 g.) was methylenated by the method described in the previously mentioned preparation of myristicin, and the neutral product distilled, b. p. 86—87°/0·2—0·18 mm. (0·6 g.). On treatment of 0·18 g. with bromine (3 ml.) at 0°, it formed tetrabromomyristicin (0·25 g.), colourless needles from alcohol, m. p. 128°, undepressed by admixture with an authentic specimen.

The identity of the methylenated material with myristicin was further confirmed by rearrangement to *iso*myristicin, and the formation of its tetrabromo-derivative, m. p. 157°, raised to 158° on admixture with authentic material, m. p. 159°.

Identification of the pyrolysis product. The above pyrolysis product (0·8 g.) was treated with methyl sulphate (3 lots of 1 ml.) in an atmosphere of hydrogen, with addition of 10% sodium hydroxide and

shaking till alkaline after each lot of methyl sulphate. The methyl ether (0·7 g.) was isolated by extraction with ether and rearranged by being heated for 48 hours on the steam-bath with potassium hydroxide (2·6 g.) and alcohol (10 ml.). Steam distillation and ether extraction of the distillate yielded an oil (0·5 g.) which was dissolved in acetone (20 ml.) and oxidised by the gradual addition of potassium permanganate (powdered; 1 g.) with shaking. Heat was evolved, and the reaction was completed by warming on the steam-bath for a few minutes. Any unchanged oil was removed by steam distillation, and sodium hydrogen sulphite and dilute sulphuric acid were added to the residual solution. The product which crystallised (0·15 g.) had m. p. 105—145° and formed colourless needles after one crystallisation from water (charcoal); m. p. 169—170°, undepressed by admixture with 3 : 4 : 5-trimethoxybenzoic acid (*O*-trimethylgallic acid).

Our thanks are due to Professor T. G. H. Jones of the University of Queensland for the gift of oil of nutmeg, and to Dr. G. Burger for most of the micro-analyses.

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[*Received, May 5th*, 1948.]

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100. *Synthetic Oestrogens related to Triphenylethylene. Part I.*

By WADIE TADROS, KASEM FARAHAT, and J. M. ROBSON.

A number of triphenylethylenes have been synthesised and tested for oestrogenic activity. Injected subcutaneously in doses of 5 mg., the new compounds 4, 5, and 6 (see Table) showed oestrogenic activity in contrast to the corresponding compounds with no halogen in the phenyl group, which are inactive in this dose. The time required for the oestrogenic activity of the new compounds 8 and 10 (see Table) to fall to half after subcutaneous injection in solution in olive oil in 100 μg. doses into ovariectomised mice is, however, shorter than that of the corresponding compounds with a phenyl group only on the ethylenic 2-carbon atom.

A NUMBER of new triphenylethylene derivatives have been prepared with the object of extending a systematic study of the effect of different substituents in the benzene nuclei on the oestrogenic activity.

By addition of different *pp'*-disubstituted benzophenones to an ethereal solution of *p*-chlorobenzylmagnesium chloride (it was not found necessary to filter this solution in the present investigation; contrast Kharasch and Weinhouse, *J. Org. Chem.*, 1936—37, **1**, 209), and decomposition of the product with aqueous ammonium chloride, the corresponding carbinols are obtained. Dehydration of the carbinols gives the triphenylethylenes, and these on bromination readily yield the corresponding triphenylbromoethylenes.

The time required for the oestrogenic activity to fall to half was measured by the method described by Robson (*Quart. J. Exp. Physiol.*, 1938, **28**, 195). The compounds were dissolved in olive oil and the oestrogenic activity was examined on injection subcutaneously and on administration orally by a stomach tube into groups of 5 ovariectomised mice (see Table). Average weight of the mice was 20—25 g.

Time required for oestrogenic activity to fall to half.

No.	Substance.	Dose (μ g.).	Time (days).
1	1 : 1-*Diphenyl*-2-p-*bromophenylethylene*	1000	2
2	2-Bromo-1 : 1-diphenyl-2-*p*-bromophenylethylene	1000	56
3	2-*Bromo*-1 : 1-*diphenyl*-2-p-*chlorophenylethylene*	100	11
4	*Bromotri*-p-*chlorophenylethylene*	5000	5
5	2-*Bromo*-2-p-*chlorophenyl*-1 : 1-*di*-p-*bromophenylethylene*	5000	10
6	2-*Bromo*-2-p-*chlorophenyl*-1 : 1-*di*-p-*iodophenylethylene*	5000	10
7	2-p-*Chlorophenyl*-1 : 1-*di*-p-*methoxyphenylethylene*	1000	3
8	2-*Bromo*-2-p-*chlorophenyl*-1 : 1-*di*-p-*methoxyphenylethylene*	100	5
	,, ,, ,, ,,	10 *	slight
	,, ,, ,, ,,	100 *	12
9	2-p-*Chlorophenyl*-1 : 1-*di*-p-*ethoxyphenylethylene*	1000	slight
10	2-*Bromo*-2-p-*chlorophenyl*-1 : 1-*di*-p-*ethoxyphenylethylene*	100	3
	,, ,, ,, ,,	10 *	3
	,, ,, ,, ,,	100 *	16
11	2-Bromo-2-phenyl-1 : 1-di-*p*-ethoxyphenylethylene (D.B.E.)	10 *	7
	,, ,, ,, ,,	50 *	21
	,, ,, ,, ,,	500 *	38

* Compounds in solution in olive oil administered orally by a stomach tube into groups of 5 ovariectomised mice. In all other cases compounds in solution in olive oil were injected subcutaneously into groups of 5 ovariectomised mice.

It is interesting to note that when injected subcutaneously in oily solution in doses of 5 mg. into groups of 5 ovariectomised mice, the compounds 4, 5, and 6 in which the three para-positions are occupied by a halogen possess oestrogenic activity, whereas the corresponding derivatives, 2-bromo-2-phenyl-1 : 1-di-*p*-chloro-bromo-, and -iodo-phenylethylene, with only the phenyl group on the ethylenic 2-carbon atom show little or no oestrogenic activity (Schönberg, Robson, Tadros, and Fahim, *J.*, 1940, 1327). The time required for the oestrogenic activity of the new compounds 8 and 10 to fall to half is, however, shorter than that of the corresponding compounds without the chlorine in the phenyl group [Schönberg, *et al.*, *loc. cit.*; Robson, Schönberg, and Tadros, *Nature*, 1942, **150**, 22 (the name of the third author was inadvertently omitted in this publication); Tadros and Schönberg, *J.*, 1943, 394], the latter of which is especially interesting as it exerts prolonged activity when administered orally. It is also remarkable that compounds 8 and 10 show more prolonged action when administered orally than when injected subcutaneously in doses of 100 μg.

Adequate discussion of the above findings is impossible before a study of the metabolism of these compounds is carried out. It has been found (Stroud, *J. Endocrinol.*, 1940, **2**, 55) that stilbene, diphenyl ether, diphenylmethane, and diphenylhexadiene undergo metabolic conversion in female rabbits, giving rise to phenolic compounds, with more potent oestrogenic activity than the corresponding mother substances, in which the hydroxyl group or groups are in the *p*-positions. It would therefore be important to study the metabolic products of the various triphenylethylenes with halogens in the *p*-positions and to correlate with their oestrogenic activity the extent to which they may be hydroxylated in the body.

The increase in potency on introducing a halogen atom into the ethylenic linkage of the triphenylethylene shown by triphenylchloroethylene (Robson, Schönberg, and Fahim, *Nature*, 1938, **142**, 292), triphenylbromoethylene, and triphenyliodoethylene (Robson, Schönberg, and Fahim, unpublished) has also been observed with the triphenylethylene derivatives tested in the present investigation.

1 : 1-Diphenyl-2-*p*-bromophenylethylene * (compound 1) was prepared by the dehydration of diphenyl-*p*-bromobenzylcarbinol (Koelsch, *J. Amer. Chem. Soc.*, 1936, **58**, 1328). On bromination, 2-bromo-1 : 1-diphenyl-2-*p*-bromophenylethylene,* m. p. 114—115°, was readily obtained. The latter, m. p. 109—110°, was obtained (Koelsch, *loc. cit.*) by direct bromination of the carbinol, the product being purified by distillation under reduced pressure followed by recrystallisation from acetic acid.

Experimental.

Diphenyl-p-*chlorobenzylcarbinol* (Kharasch and Weinhouse, *loc. cit.*).—To the Grignard reagent prepared from magnesium (2·85 g.), *p*-chlorobenzyl chloride (20 g.), and ether (100 c.c.), benzophenone (12 g.) was added; after two hours' stirring the solution was left overnight and then decomposed with cold aqueous ammonium chloride. Ether extracted the carbinol which separated from petroleum (b. p. 100—110°) in colourless crystals, m. p. 116°. The yield of this and the 12 following compounds were almost theoretical (Found : C, 77·8; H, 5·6; Cl, 11·4. Calc. for $C_{20}H_{17}OCl$: C, 77·8; H, 5·5; Cl, 11·5%).

Di-p-*chlorophenyl*-p-*chlorobenzylcarbinol*, similarly prepared (magnesium 2 g., *p*-chlorobenzyl chloride 14 g., ether 100 c.c.; *pp'*-dichlorobenzophenone 10 g.), was obtained in colourless crystals, m. p. 100—102° (Found : C, 63·6; H, 4·0; Cl, 28·1. $C_{20}H_{15}OCl_3$ requires C, 63·6; H, 4·0; Cl, 28·2%).

Di-p-*bromophenyl*-p-*chlorobenzylcarbinol*, similarly prepared (magnesium 1·7 g., *p*-chlorobenzyl chloride 12 g., ether 100 c.c.; *pp'*-dibromobenzophenone 10 g.), was obtained in almost colourless crystals, m. p. 126—128° (Found : C, 52·1; H, 3·4; Cl, 7·6; Br, 34·4. $C_{20}H_{15}OClBr_2$ requires C, 51·4; H, 3·2; Cl, 7·6; Br, 34·3%).

Di-p-*iodophenyl*-p-*chlorobenzylcarbinol*, similarly prepared (magnesium 0·7 g., *p*-chlorobenzyl chloride 5 g., ether 50 c.c.; *pp'*-di-iodobenzophenone 5 g.), was obtained in pale straw-yellow or colourless crystals, sintering at 155°, m. p. 164° (Found : C, 43·3; H, 2·7; Cl, 6·3; I, 44·9. $C_{20}H_{15}OClI_2$ requires C, 42·8; H, 2·7; Cl, 6·3; I, 45·3%).

Di-p-*methoxyphenyl*-p-*chlorobenzylcarbinol*, similarly prepared (magnesium 2 g., *p*-chlorobenzyl chloride 14 g., ether 100 c.c.; *pp'*-dimethoxybenzophenone 10 g.), was obtained in colourless crystals, m. p. 116—117° (Found : C, 71·7; H, 5·7; Cl, 9·8. $C_{22}H_{21}O_3Cl$ requires C, 71·6; H, 5·7; Cl, 9·6%).

Di-p-*ethoxyphenyl*-p-*chlorobenzylcarbinol*, similarly prepared (magnesium 2 g., *p*-chlorobenzyl chloride 14 g., ether 100 c.c.; *pp'*-diethoxybenzophenone 10 g.), was obtained in colourless crystals m. p. 108° (Found : C, 72·8; H, 6·4. $C_{24}H_{25}O_3Cl$ requires C, 72·6; H, 6·3%).

1 : 1-*Diphenyl*-2-p-*chlorophenylethylene*.—This *compound* was obtained by vacuum distillation of diphenyl-*p*-chlorobenzylcarbinol (10 g.) in presence of one drop of 20% sulphuric acid. The oily distillate which solidified on cooling separated from alcohol in colourless crystals, m. p. 76—77° (Found : C, 82·7; H, 5·3; Cl, 12·3. $C_{20}H_{15}Cl$ requires C, 82·6; H, 5·2; Cl, 12·2%).

Tri-p-*chlorophenylethylene*.—A solution of di-*p*-chlorophenyl-*p*-chlorobenzylcarbinol (3 g.) in glacial acetic (20 c.c.) and concentrated sulphuric acid (1 c.c.) was refluxed for an hour, then poured into cold water, left overnight, and the precipitate filtered off and washed with water. The *compound* separated

* Prepared by (Miss) Tahia El Sayed Ali, Fouad I University, Cairo, Egypt.

from ethyl alcohol in colourless crystals, m. p. 90—91° (Found: C, 66·8; H, 3·9; Cl, 29·7. $C_{20}H_{13}Cl_3$ requires C, 66·8; H, 3·6; Cl, 29·6%).

2-p-*Chlorophenyl*-1 : 1-*di*-p-*bromophenylethylene*, similarly prepared from di-*p*-bromophenyl-*p*-chlorobenzylcarbinol, separated from ethyl alcohol in colourless crystals, m. p. 84° (Found: C, 53·7; H, 3·0; Cl, 7·9; Br, 35·8. $C_{20}H_{13}ClBr_2$ requires C, 53·5; H, 2·9; Cl, 7·9; Br, 35·7%).

2-p-*Chlorophenyl*-1 : 1-*di*-p-*iodophenylethylene*, similarly prepared from di-*p*-iodophenyl-*p*-chlorobenzylcarbinol (4 g.), glacial acetic acid (60 c.c.), and conc. sulphuric acid (2·5 c.c.) (3 hours' heating), crystallised from acetic acid or petroleum (b. p. 50—60°) in colourless crystals, m. p. 102—103° (Found: C, 44·4; H, 2·5; Cl, 6·5; I, 46·7. $C_{20}H_{13}ClI_2$ requires C, 44·2; H, 2·4; Cl, 6·5; I, 46·8%).

1 : 1-*Diphenyl*-2-p-*bromophenylethylene* was similarly prepared from diphenyl-*p*-bromobenzylcarbinol (Koelsch, *loc. cit.*) (2 g.), glacial acetic acid (15 c.c.), and concentrated sulphuric acid (0·2 c.c.) (45 minutes heating). On adding the concentrated sulphuric acid to the carbinol in acetic acid, a green colour developed, which changed gradually on heating to bluish-green. The compound separated from ethyl alcohol in colourless crystals, m. p. 77° (Found: C, 71·8; H, 4·6; Br, 23·3. $C_{20}H_{15}Br$ requires C, 71·6; H, 4·5; Br, 23·9%).

2-p-*Chlorophenyl*-1 : 1-*di*-p-*methoxyphenylethylene*.—(*a*) A solution of di-*p*-methoxyphenyl-*p*-chlorobenzylcarbinol (3 g.) in glacial acetic acid (20 c.c.) and concentrated sulphuric acid (1 c.c.) was refluxed for 45 minutes and then treated as above. The *compound* separated from ethyl alcohol in colourless crystals, m. p. 91°. On addition of the sulphuric acid to the carbinol in glacial acetic acid, a dark violet colour developed. (*b*) The ethylenic compound was also obtained from the carbinol (5 g.) by vacuum distillation in presence of one drop of 20% sulphuric acid. On heating, a greenish-blue colour developed, changing gradually to blue, and before distillation the colour became very pale brown. The compound separated from ethyl alcohol in colourless crystals, m. p. 91° (Found: C, 75·3; H, 5·5. $C_{22}H_{19}O_2Cl$ requires C, 75·3; H, 5·4%).

2-p-*Chlorophenyl*-1 : 1-*di*-p-*ethoxyphenylethylene* was obtained from di-*p*-ethoxyphenyl-*p*-chlorobenzylcarbinol (10 g.) by vacuum distillation in presence of one drop of 20% sulphuric acid. The same display in colour as in (*b*) above took place. The compound separated from ethyl alcohol in colourless crystals, m. p. 76° (Found: C, 76·2; H, 6·3; Cl, 9·7. $C_{24}H_{23}O_2Cl$ requires C, 76·1; H, 6·1; Cl, 9·4%).

2-*Bromo*-1 : 1-*diphenyl*-2-p-*chlorophenylethylene*.—A solution of bromine (0·6 g.) in glacial acetic acid (10 c.c.) was added to a solution of 1 : 1-diphenyl-2-*p*-chlorophenylethylene (1·1 g.) in the same solvent (10 c.c.). The solution was refluxed for an hour and then cooled, and the crystalline precipitate recrystallised from ethyl alcohol from which the *compound* separated in straw-yellow crystals, m. p. 114—115° (Found: C, 64·6; H, 3·9; Cl, 9·6; Br, 21·6. $C_{20}H_{14}ClBr$ requires C, 65·0; H, 3·8; Cl, 9·6; Br, 21·7%).

Bromotri-p-*chlorophenylethylene*, similarly prepared (bromine 0·9 g., in acetic acid 10 c.c.; tri-*p*-chlorophenylethylene 2 g. in acetic acid 20 c.c.), formed colourless crystals, m. p. 166° (Found: C, 54·8; H, 2·9; Cl, 24·4; Br, 18·3. $C_{20}H_{12}Cl_3Br$ requires C, 54·7; H, 2·7; Cl, 24·3; Br, 18·2%).

2-*Bromo*-2-p-*chlorophenyl*-1 : 1-*di*-p-*bromophenylethylene*, similarly prepared (0·8 g. bromine in 10 c.c. glacial acetic acid; 2-*p*-chlorophenyl-1 : 1-di-*p*-bromophenylethylene 2 g., in acetic acid 10 c.c.), formed almost colourless crystals, m. p. 168° (Found: C, 46·0; H, 2·4; Cl, 6·7; Br, 45·5. $C_{20}H_{12}ClBr_3$ requires C, 45·5; H, 2·3; Cl, 6·7; Br, 45·5%).

2-*Bromo*-2-p-*chlorophenyl*-1 : 1-*di*-p-*iodophenylethylene* was similarly prepared (bromine 0·5 g. in acetic acid 10 c.c.; 2-*p*-chlorophenyl-1 : 1-di-*p*-iodophenylethylene 1·75 g. in acetic acid 20 c.c.); it separated from acetic acid in straw-yellow crystals, m. p. 158—160° (Found: C, 39·3; H, 2·0; 5·45 mg. gave 7·38 mg. of silver halide. $C_{20}H_{12}ClBrI_2$ requires C, 38·6; H, 1·9%; 7·19 mg. of silver halide).

2-*Bromo*-2-p-*chlorophenyl*-1 : 1-*di*-p-*methoxyphenylethylene*, similarly prepared (bromine 0·8 g. in acetic acid 10 c.c.; 2-*p*-chlorophenyl-1 : 1-di-*p*-methoxyphenylethylene 2 g. in acetic acid 10 c.c.), recrystallised from ethyl alcohol in colourless crystals, m. p. 112° (Found: C, 61·5; H, 4·3; Cl, 8·4; Br, 18·9. $C_{22}H_{18}O_2ClBr$ requires C, 61·5; H, 4·2; Cl, 8·3; Br, 18·6%).

2-*Bromo*-2-p-*chlorophenyl*-1 : 1-*di*-p-*ethoxyphenylethylene*, similarly prepared, was obtained in colourless crystals, m. p. 98° (Found: C, 63·0; H, 4·9; Cl, 7·8; Br, 17·7. $C_{24}H_{22}O_2ClBr$ requires C, 63·0; H, 4·8; Cl, 7·8; Br, 17·5%).

2-Bromo-1 : 1-diphenyl-2-*p*-bromophenylethylene, similarly prepared (0·22 g. bromine in 5 c.c. acetic acid; 1 : 1-diphenyl-2-*p*-bromophenylethylene 0·5 g. in acetic acid 15 c.c.), was obtained in very pale straw-coloured crystals, m. p. 114—115° (Koelsch, *loc. cit.*, gave m. p. 109—110°) (Found: Br, 38·4. Calc. for $C_{20}H_{14}Br_2$: Br, 38·4%).

Thanks of two of us (W. T. and K. F.) are due to Professor A. Schönberg for his interest in the progress of the work. The expenses of this investigation were, in part, defrayed by a grant from the Medical Research Council (To J. M. R.).

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101. *Synthetic Oestrogens related to Triphenylethylene. Part II.*

By Wadie Tadros.

2-Phenyl-1 : 1-di-*p*-hydroxyphenylethylene is readily obtained by heating compounds 3 and 7 (see Table) in a vacuum in presence of a trace of sulphuric acid or by refluxing their solutions in acetic acid in presence of sulphuric or hydrobromic acid. *2-Bromo-2-phenyl-1 : 1-di-p-hydroxyphenylethylene* is readily obtained by refluxing a solution of *2-bromo-2-phenyl-1 : 1-di*-p-iso*propoxyphenylethylene* in acetic acid in presence of sulphuric acid. This and its diacetate which can be readily obtained by bromination of *2-phenyl-1 : 1-di*-p-*acetoxyphenylethylene* have been shown to be highly active oestrogenic compounds (Tadros and Robson, *Nature*, 1947, **160**, 20). Some new triphenylchloroethylenes were prepared by chlorinating their corresponding ethylenes. *Di*-p-*ethylthiophenylbenzylcarbinol* and *di*-p-n-*propylthiophenylbenzylcarbinol* are obtained by adding the appropriate ketone to the ethereal solution of benzylmagnesium chloride.

Injected subcutaneously in oily solution into ovariectomised mice, *2-bromo-2-phenyl-1 : 1-di*-p-*hydroxyphenylethylene* has been found (Tadros and Robson, *loc. cit.*) to possess high oestrogenic activity; but the duration time, like that of diethylstilboestrol (Dodds, Golberg, Lawson, and Robinson, *Proc. Roy. Soc.*, 1939, **127**, *B*, 140), is not appreciably increased with increased dosage.

2-Bromo-2-phenyl-1 : 1-di-*p*-acetoxyphenylethylene (Tadros and Robson, *loc. cit.*) shows more prolonged action, and its minimal effective dose is lower. Some points of interest have been noted on the preparation of the 2-bromo-2-phenyl-1 : 1-di-*p*-hydroxyphenylethylene and 2-phenyl-1 : 1-di-*p*-hydroxyphenylethylene, the latter first prepared (Dodds *et al.*, *loc. cit.*) by demethylation of 2-phenyl-1 : 1-di-*p*-methoxyphenylethylene. Comment on the findings and a discussion of the mechanism of reaction or reactions involved are, however, deferred until work in progress has been completed.

Addition of *pp'*-disubstituted benzophenones to an ethereal solution of benzylmagnesium chloride, and decomposition of the products with aqueous ammonium chloride, give rise to the corresponding carbinols when the substituent is methoxy- (Koelsch, *J. Amer. Chem. Soc.*, 1932, **54**, 2487; cf. Orekhoff, *Bull. Soc. chim.*, 1919, **25**, 174) or ethoxy- (Tadros and Schönberg, *J.*, 1943, 394) (see Table). In the present communication it is shown (Table) that under the same

Ketone.	Product.
pp'-Dimethoxybenzophenone.	Di-*p*-methoxyphenylbenzylcarbinol (1).
pp'-Diethoxybenzophenone.	Di-*p*-ethoxyphenylbenzylcarbinol (2).
pp'-*Dibenzyloxybenzophenone.*	*Di*-p-*benzyloxyphenylbenzylcarbinol* (3).
pp'-*Diethylthiobenzophenone.*	*Di*-p-*ethylthiophenylbenzylcarbinol* (4).
pp'-*Di*-n-*propylthiobenzophenone.*	*Di*-p-n-*propylthiophenylbenzylcarbinol* (5).
pp'-Di-*n*-propoxybenzophenone.	*2-Phenyl*-1 : 1-*di*-p-n-*propoxyphenylethylene* (6).
pp'-Di-*iso*propoxybenzophenone.	*2-Phenyl*-1 : 1-*di*-p-iso*propoxyphenylethylene* (7).
pp'-*Diallyloxybenzophenone.*	*2-Phenyl*-1 : 1-*di*-p-*allyloxyphenylethylene* (8).

experimental conditions the carbinols are similarly obtained when the substituent is benzyloxy-, ethylthio-, or *n*-propylthio-, whereas the corresponding triphenylethylenes are directly isolated when it is *n*-propoxy-, *iso*propoxy-, or allyloxy-.

4-*iso*Propoxystilbene is also directly isolated after the addition of *p-iso*propoxybenzaldehyde to the same Grignard reagent and decomposition of the product with aqeuous ammonium chloride.

2-Phenyl-1 : 1-di-*p*-hydroxyphenylethylene is obtained by heating compound 3 or 7 (Table) in a vacuum in presence of one drop of 10 or 20% sulphuric acid, or by refluxing its solution in acetic acid in presence of sulphuric or hydrobromic acid. A red colour develops always on heating.

As a result of the cleavage of one ether linkage only, intermediary *cis*- and *trans*-derivatives would be formed.

2-Bromo-2-phenyl-1 : 1-di-*p*-hydroxyphenylethylene is readily obtained by refluxing a solution of 2-bromo-2-phenyl-1 : 1-di-*p*-isopropoxyphenylethylene in acetic acid in presence of sulphuric acid.

pp'-Diethylthiobenzophenone was prepared by the Friedel–Crafts reaction or by the method by which Schönberg (*Annalen*, 1923—24, **436**, 205) obtained *pp'*-dimethylthiobenzophenone. *pp'*-Diethylthiobenzophenone and *pp'*-di-*n*-propylthiobenzophenone have thus been obtained when thiophenetole or phenyl *n*-propyl sulphide was caused to react with oxalyl chloride in carbon disulphide by adding anhydrous aluminium chloride.

2-Chloro-2-phenyl-1 : 1-*di*-p-*ethoxyphenyl*-, -*di*-p-n-*propoxyphenyl*-, and *di*-p-iso*propoxy*-

phenyl-ethylene were prepared by adding slightly less than the requisite molar quantity of chlorine in acetic acid to a solution of the corresponding ethylenic compound in the same solvent. 2-Chloro-2-phenyl-1 : 1-di-*p*-ethoxyphenylethylene was also prepared by chlorinating the ethylenic compound with sulphuryl chloride in presence of a little benzoyl peroxide.

Experimental.

pp'-*Diallylbenzophenone*, prepared from *pp'*-dihydroxybenzophenone (30 g.) (Jones, *J.*, 1936, 1854), allyl iodide (60 g.), and alcoholic sodium ethoxide (6·4 g. of sodium added to 200 c.c. of absolute alcohol), separated from alcohol in colourless crystals, m. p. 128—130° (Found : C, 77·4; H, 6·1. $C_{19}H_{18}O_2$ requires C, 77·5; H, 6·1%).

pp'-*Dibenzyloxybenzophenone*, similarly prepared using equivalent quantity of benzyl bromide, separated from benzene or absolute alcohol in colourless crystals, m. p. 186—188° (Found : C, 81·7; H, 5·5. $C_{27}H_{22}O_3$ requires C, 82·2; H, 5·6%).

pp'-Diethoxybenzophenone, m. p. 130—131° (Jones, *loc. cit.*), was readily obtained by the Friedel–Crafts condensation of *p*-ethoxybenzoyl chloride (520 g.), phenetole (1 kg.), and aluminium chloride (800 g.) (yield *ca.* 80%).

pp'-*Diethylthiobenzophenone*. (*a*) Aluminium chloride (18 g.) was gradually added to an ice-cooled mixture of thiophenetole (32 g.) and *p*-ethylthiobenzoyl chloride (Donleavy and English, *J. Amer. Chem. Soc.*, 1940, **62**, 220) [from *p*-ethylthiobenzoic acid (14 g.) and phosphorus pentachloride (16·5 g.)]. The black mixture was subsequently heated on the water-bath for 20 minutes, decomposed with ice, and excess of thiophenetole steam distilled. The ketone separated from alcohol in pale greenish crystals which sintered at 113°, m. p. 117—118°.

(*b*) To a cooled (ice–salt) solution of thiophenetole (13 g.), and oxalyl chloride (6·4 g.) in carbon disulphide (50 c.c.), aluminium chloride (15 g.) was gradually added. The solution was left at room temperature for 3 hours and then heated at 35° for 1 hour. The carbon disulphide was poured off and the dark brown residue treated with ice. The *ketone* thus obtained separated from alcohol in pale greenish plates which sintered at 113°, m. p. 117—118° (Found : C, 67·8; H, 6·2; S, 20·6. $C_{17}H_{18}OS_2$ requires C, 67·6; H, 6·0; S, 21·2%).

pp'-*Di*-n-*propylthiobenzophenone*, similarly prepared as in (*b*) above (phenyl *n*-propyl sulphide, 15·2 g.; oxalyl chloride, 6·4 g.; carbon disulphide, 70 c.c.; anhydrous aluminium chloride, 15 g.) and crystallised, was obtained in colourless crystals which sintered at 62°, m. p. 65—66° (Found : C, 69·5; H, 6·7; S, 19·0. $C_{19}H_{22}OS_2$ requires C, 69·1; H, 6·7; S, 19·4%).

The following carbinols were prepared by adding the appropriate *pp'*-disubstituted benzophenone (0·5 mole) to the Grignard reagent prepared from magnesium (1 atom), benzyl chloride (1 mole), and ether (1800 c.c.), stirring for 4 hours, leaving overnight, then decomposing the products with aqueous ammonium chloride, extracting with ether or benzene–ether, and crystallising from petroleum (b. p. 100—110°) from which they separated in colourless crystals, the yields being almost theoretical. *Di*-p-*benzyloxyphenylbenzylcarbinol* lost consistency at 132°, and had m. p. 136° (Found : C, 84·1; H, 6·2. $C_{34}H_{30}O_3$ requires C, 84·0; H, 6·2%). *Di*-p-*ethylthiophenylbenzylcarbinol* had m. p. 94—96° (Found : C, 72·8; H, 6·5; S, 16·0. $C_{34}H_{36}OS_2$ requires C, 73·1; H, 6·6; S, 16·2%). *Di*-p-n-*propylthiophenylbenzylcarbinol* had m. p. 90—92° (Found : C, 73·8; H, 7·2; S, 15·4. $C_{36}H_{30}OS_2$ requires C, 74·0; H, 7·1; S, 15·2%).

The following ethylenes were isolated in colourless crystals and in almost theoretical yields on attempting the preparation of the corresponding carbinols as above; they were crystallised from alcohol : 2-*phenyl*-1 : 1-*di*-p-*allyloxyphenylethylene*, m. p. 71—73° (Found : C, 84·8; H, 6·7. $C_{26}H_{24}O_2$ requires C, 84·8; H, 6·5%); 2-*phenyl*-1 : 1-*di*-p-n-*propoxyphenylethylene*, m. p. 76—77° (when heated in vacuum in presence of 1 drop of 20% sulphuric acid, the compound distilled unchanged) (Found : C, 83·8; H, 7·7. $C_{26}H_{28}O_2$ requires C, 83·9; H, 7·5%); 2-*phenyl*-1 : 1-*di*-p-iso*propoxyphenylethylene*, m. p. 83—84° (Found : C, 83·7; H, 7·5. $C_{26}H_{28}O_2$ requires C, 83·9; H, 7·5%).

2-*Phenyl*-1 : 1-*di*-p-*benzyloxyphenylethylene* was obtained in almost theoretical yield by heating di-*p*-benzyloxyphenylbenzylcarbinol (5 g.) alone or in presence of 1 drop of 10% sulphuric acid in a vacuum in an oil-bath at 170—175° for about 10 minutes. On cooling, the substance solidified; it separated from alcohol in colourless crystals which sintered at 88°, m. p. 94° (Found : C, 86·7; H, 6·0. $C_{34}H_{28}O_2$ requires C, 87·2; H, 6·0%).

2-*Phenyl*-1 : 1-*di*-p-*hydroxyphenylethylene*. (*a*) A solution of either 2-phenyl-1 : 1-di-*p*-*iso*propoxyphenylethylene (5 g.) or di-*p*-benzyloxyphenylbenzylcarbinol (7 g.) in glacial acetic (49 c.c.), water (1 c.c.), and concentrated sulphuric acid (2 c.c.) was refluxed on a sand-bath, the former for 3 hours and the latter for 10 minutes. The red solutions were then diluted with cold water and left in the ice-chest overnight. The precipitate was dissolved in 2—3% sodium hydroxide solution. The violet alkaline solution was either filtered or extracted with benzene–ether, and the phenolic compound was precipitated in the usual manner. It separated from benzene in almost colourless crystals (yield *ca.* 60—70%) (Found : C, 83·3; H, 5·5. Calc. for $C_{20}H_{16}O_2$: C, 83·3; H, 5·6%).

(*b*) A solution of di-*p*-benzyloxyphenylbenzylcarbinol (5 g.) in glacial acetic acid (50 c.c.), and hydrobromic acid (*d* 1·49; 10 c.c.) was refluxed on a sand-bath for 1 hour. The red solution was then diluted with water, made slightly alkaline, and extracted with ether. This extract contained benzyl bromide, b. p. 196°. The violet alkaline solution was treated as above, and 2-phenyl-1 : 1-di-*p*-hydroxyphenylethylene, m. p. 178°, was isolated in *ca.* 60% yield.

(*c*) 2-Phenyl-1 : 1-di-*p*-*iso*propoxyphenylethylene (10 g.), to which a drop of 20% sulphuric acid was added, was heated in a vacuum in an oil-bath at 220—230° for about 5 minutes. A pink colour developed with rise of temperature, but subsequently faded. The substance was then dissolved in aqueous sodium hydroxide and treated as above, and the above phenolic compound, m. p. 178°, was obtained.

(*d*) On heating di-*p*-benzyloxyphenylcarbinol (5 g.) in presence of 1 drop of 10% sulphuric acid in a

vacuum at 190° for about 10 minutes, and then cooling, the substance set into a glassy mass from which the above compound, m. p. 178°, was extracted with 1% aqueous sodium hydroxide. The carbinol became rose-coloured when heated, but turned bluish-green at 220—230°; the products will be investigated.

2-*Phenyl*-1 : 1-*di*-p-*acetoxyphenylethylene*. A solution of 2-phenyl-1 : 1-di-*p*-hydroxyphenylethylene (2·5 g.) in acetic anhydride (25 c.c.) was refluxed on a sand-bath for 1 hour. The solution was diluted with cold water and left overnight in the ice-chest. The semi-solid *product* separated from methyl alcohol in colourless crystals, m. p. 84° (yield almost theoretical) (Found: C, 77·4; H, 5·4. $C_{24}H_{20}O_4$ requires C, 77·4; H, 5·4%).

2-*Phenyl*-1 : 1-*di*-p-*propionyloxyphenylethylene*, similarly prepared using propionic anhydride and refluxing for 2 hours, separated from ether–petroleum (b. p. 50—60°) or methyl alcohol in colourless crystals which sintered at 62°, m. p. 65—66° (yield *ca.* 90%) (Found: C, 78·1; H, 6·1. $C_{26}H_{24}O_4$ requires C, 78·0; H, 6·0%).

4-*isoPropoxystilbene*. On adding *p-iso*propoxybenzaldehyde to an ethereal solution of benzylmagnesium chloride and treating the product as above, a colourless crystalline substance, m. p. 115—116°, separated from alcohol. Repeated fractional recrystallisation of the material gave the same substance, m. p. 115—116°. The substance was either the *cis*- or the *trans*-form of 4-iso*propoxystilbene* (Found: C, 85·1; H, 7·5. $C_{17}H_{18}O$ requires C, 85·7; H, 7·6%).

2-*Chloro*-2-*phenyl*-1 : 1-*di*-p-*ethoxyphenylethylene*. (*a*) Sulphuryl chloride (8 g.) was added to a solution of 2-phenyl-1 : 1-di-*p*-ethoxyphenylethylene (15 g.) in glacial acetic acid (60 c.c.) containing benzoyl peroxide (0·06 g.). The vigorous reaction was controlled by dipping the flask in cold water. After ½ hour on a bath at 70—75°, the solution was diluted with water, and the precipitate recrystallised from alcohol from which it separated in colourless crystals, m. p. 86—88° (Found: C, 75·5; H, 6·1; Cl, 9·2. $C_{24}H_{23}O_3Cl$ requires C, 76·1; H, 6·1; Cl, 9·4%).

(*b*) A solution of chlorine (0·9 g.) in acetic acid (35 c.c.) was added to a solution of 2-phenyl-1 : 1-di-*p*-ethoxyphenylethylene (5 g.) in the same solvent (20 c.c.). The solution was refluxed on a sand-bath for 2 hours. It was then diluted with water, and the precipitate recrystallised from methyl alcohol from which it separated in colourless crystals, m. p. 86—88°.

The following chloro- and bromo-ethylenes were prepared by adding a solution of slightly less than the requisite molar quantity of the halogen [as in (*b*) above] in acetic acid to the ethylene dissolved in the same solvent. The solutions were subsequently diluted with water, and the precipitates dissolved in alcohol. The alcoholic solutions were refluxed on the water-bath for 1—1½ hours. On cooling, the halogen derivatives separated in colourless crystals. 2-*Chloro*-2-*phenyl*-1 : 1-*di*-p-n-*propoxyphenylethylene* sintered at 99°, m. p. 102° (Found: C, 77·0; H, 6·9; Cl, 9·0. $C_{26}H_{27}O_2Cl$ requires C, 76·8; H, 6·6; Cl, 8·7%). 2-*Chloro*-2-*phenyl*-1 : 1-*di*-p-iso*propoxyphenylethylene* sintered at 102°, m. p. 106° (Found: C, 76·6; H, 7·1; Cl, 9·2. $C_{26}H_{27}O_2Cl$ requires C, 76·8; H, 6·6; Cl, 8·7%). 2-*Bromo*-2-*phenyl*-1 : 1-*di*-p-n-*propoxyphenylethylene* had m. p. 101° (Found: C, 69·4; H, 6·1; Br, 18·1. $C_{26}H_{27}O_2Br$ requires C, 69·2; H, 6·0; Br, 17·7%). 2-*Bromo*-2-*phenyl*-1 : 1-*di*-p-iso*propoxyphenylethylene* had m. p. 119—120° (Found: C, 69·6; H, 6·2; Br, 17·5. $C_{26}H_{27}O_2Br$ requires C, 69·2; H, 6·0; Br, 17·7%).

2-*Bromo*-2-*phenyl*-1 : 1-*di*-p-*acetoxyphenylethylene*. A solution of bromine (0·43 g.) in acetic acid (5 c.c.) was added to a solution of 2-phenyl-1 : 1-di-*p*-acetoxyphenylethylene (1 g.) in the same solvent (15 c.c.). Acetic anhydride (5 c.c.) was added and the mixture refluxed on the sand-bath for 45 minutes. The *bromo*-compound which was precipitated on dilution with iced water separated from methyl alcohol in colourless crystals, m. p. 157—159° (Found: C, 63·6; H, 4·3; Br, 18·0. $C_{24}H_{19}O_4Br$ requires C, 63·9; H, 4·2; Br, 17·7%).

2-*Bromo*-2-*phenyl*-1 : 1-*di*-p-*hydroxyphenylethylene*. To a solution of 2-bromo-2-phenyl-1 : 1-di-*p-iso*propoxyphenylethylene (2 g.) in glacial acetic acid (19·6 c.c.) and water (0·4 c.c.) was added concentrated sulphuric acid (0·8 c.c.), and the mixture was refluxed for 1 hour. A rosy red colour which developed on heating gradually changed to red. The solution was then diluted with water and made slightly alkaline. The violet alkaline solution was either filtered or extracted with ether–benzene, and the phenolic compound was precipitated in the usual manner; it separated from benzene in very pale yellow crystals, m. p. 205—207° (Found: C, 65·9; H, 4·3; Br, 22·0. $C_{20}H_{15}O_2Br$ requires C, 65·4; H, 4·1; Br, 21·8%).

I am grateful to Professor E. E. Turner, F.R.S., for offering facilities to carry out chemical work in the Chemistry Department, Bedford College, University of London, during my stay in England.

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[*Received, August 25th*, 1947.]

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102. *The Non-saponifiable Matter of Shea Nut Fat. Part IV.* A New Tetracyclic Diethenoid Alcohol, Butyrospermol.*

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Although it has been studied intensively for a number of years, the structure of β-amyrin, parent of a considerable number of naturally occurring members of the triterpene series, has yet to be completely elucidated. The determination of the structure of the tetracyclic alcohol, basseol, isolated from alleged shea nut fat in 1934 and subsequently shown to be cyclised easily to β-amyrin, is thus of considerable importance. In order to obtain fresh supplies of basseol, the

* Part II, Beynon, Heilbron, and Spring, *J.*, 1937, 987; Part III, *idem*, *Nature*, 1938, **142**, 434.

non-saponifiable portion of shea nut fat has been re-examined with the result that the acetate of an isomeric alcohol, butyrospermol, has been isolated from the fractions of the acetylated material which should have contained basseol acetate. Butyrospermol, like basseol, is a secondary alcohol containing two ethylenic linkages, one of which is extremely readily hydrogenated but, in sharp contrast, it cannot be converted into β-amyrin, and on ozonolysis it gives acetone as the volatile fragment instead of the formaldehyde obtained from basseol.

In Part I (Heilbron, Moffet, and Spring, *J.*, 1934, 1583), the isolation of a tetracyclic diethenoid alcohol, basseol, from the non-saponifiable matter of shea nut fat was described. Originally there was some doubt as to whether the new alcohol belonged to the steroid or the triterpene series but subsequently (Beynon, Heilbron, and Spring, *J.*, 1937, 989) its classification as a triterpene alcohol was proved conclusively by the discovery of its remarkable property of isomerising in the presence of acidic reagents to the well-known mono-unsaturated pentacyclic triterpene alcohol, β-amyrin. Investigation of the structure of basseol immediately assumed much importance since it seemed to afford the opportunity of obtaining information concerning the carbon skeleton of the β-amyrin ring system which has hitherto been extremely difficult to adduce. Moreover, since as a result of the brilliant researches of Ruzicka and his collaborators, the relationship between β-amyrin and a considerable number of triterpene alcohols and acids, now known as the β-amyrin or oleanolic acid group, has been clearly established (for a summary of the interconversions in this group, see Spring, *Ann. Reports*, 1941, **38**, 191), elucidation of the basseol structure, and hence that of β-amyrin, would furnish the key to the whole group.

Work was continued in various directions on the structure of basseol in these laboratories, but owing to its interruption by the war much remained incomplete. Selenium dehydrogenation of basseol was reported (Beynon, Heilbron, and Spring, *Nature*, 1938, **142**, 434) to give a phenanthrene homologue (probably a trimethylphenanthrene) which appeared to be identical with that obtained by Ruzicka, Hösli, and Ehmann (*Helv. Chim. Acta*, 1934, **17**, 442) by selenium dehydrogenation of hederagenin, a member of the β-amyrin group, and later identified (Ruzicka and Smith, *Chem. and Ind.*, 1938, 1210) as 1 : 2 : 6-trimethylphenanthrene. Later attempts to reinvestigate the dehydrogenation of basseol were less successful and it is not impossible that the material under investigation was in fact an impure sample.

In view of the potential importance of the problem this work was resumed as soon as possible after the cessation of hostilities, a lapse of six years. Two samples of shea nut fat were obtained, one (Sample A) from a commercial source with the assistance of the Ministry of Food, the other (Sample B) directly from West Africa through the Crown Agents for the Colonies.

Sample A was saponified in bulk with alcoholic potassium hydroxide giving about 6% of non-saponifiable matter. This was acetylated with boiling acetic anhydride, and a large crop of sticky, semi-crystalline material separated on cooling. The mother-liquors were cooled to below 0° whereupon a smaller crop of solid separated which in previous work had been found to consist essentially of basseol acetate (m. p. 141°, $[\alpha]_D^{18°}$ +22°).

This second crop was crystallised twice from ethyl acetate yielding long prisms, m. p. 139—141°, $[\alpha]_D^{17°}$ +23°, which gave a brown colour with strong green fluorescence in the Liebermann–Burchard test, thus corresponding in superficial properties to basseol acetate (see Table I). Observation of the melting point on the Kofler micro-melting point stage, however, revealed that although the bulk of the material melted at about 140°, crystalline fragments persisted in the melt above this temperature, finally disappearing at 180—200°. Repeated crystallisation eventually gave a least soluble fraction, m. p. 146·5—147·5°, $[\alpha]_D^{20°}$ +11° (±2°), giving the same colour reaction in the Liebermann–Burchard test as the impure material. Further crystallisation brought about no change in either melting point or specific rotation. Chromatography of the crude acetate ($[\alpha]_D$ +23°) gave a least strongly adsorbed fraction, $[\alpha]_D^{19°}$ +11°, later fractions having increasingly higher positive rotations and extended melting points similar to the starting material. The *acetate*, m. p. 146·5—147·5°, $[\alpha]_D^{20°}$ +11°, thus appeared to be a pure compound quite distinct from, but isomeric with, basseol acetate.

Hydrolysis of the acetate gave an *alcohol*, $C_{30}H_{50}O$, and thence a *benzoate*. Oxidation of the alcohol either under mild conditions with chromium trioxide or by the Oppenauer method using benzoquinone as the hydrogen acceptor (Wettstein, *Helv. Chim. Acta*, 1940, **23**, 388) gave a *ketone* (light absorption, $\lambda_{max.}$ 2650 A., ε = 500). Titration of the acetate with perbenzoic acid revealed the presence of two ethylenic linkages, and the absence of any high-intensity light absorption above 2200 A. indicated that these were not conjugated. When the alcohol was hydrogenated using a palladium on calcium carbonate catalyst at room temperature and pressure only one molecular proportion of hydrogen was absorbed to give the *dihydro-alcohol*, from which were obtained the *dihydro-acetate* and *-benzoate*. Oxidation of the dihydro-

alcohol with chromium trioxide gave a *dihydro-ketone* which, on reduction with sodium in alcohol, regenerated the dihydro-alcohol, identified as its acetate. The ease of hydrogenation of the alcohol under such mild conditions is noteworthy, the use of a platinum catalyst and acetic acid solutions having been found necessary by previous workers with similar compounds (*e.g.*, basseol, Beynon, Heilbron, and Spring, *loc. cit.*; euphol, Newbold and Spring, *J.*, 1944, 249; cryptosterol, Marker, Wittle, and Mixon, *J. Amer. Chem. Soc.*, 1937, **59**, 1368). The dihydro-acetate (also obtained by hydrogenation of the acetate in ethyl acetate solution at room temperature and pressure with a platinum catalyst) showed only one double bond on perbenzoic acid titration and gave a pale yellow colour with tetranitromethane. In the Liebermann–Burchard test it gave a pale yellow colour with green fluorescence.

As can be seen from Table I, the compounds now described differ noticeably in their physical properties from basseol and its derivatives. It was not possible to carry out mixed melting points between comparable compounds of the two series since all available samples of basseol and its esters were found to have changed on keeping.

The physical evidence given in Table I shows fairly conclusively that the new alcohol, tentatively named butyrospermol (from the name of the shea tree, *Butyrospermum parkii*, formerly *Bassia parkii*), differs from basseol. The chemical evidence removes any shadow of doubt as to this difference.

TABLE I.

	Basseol.		Butyrospermol.	
	M. p.	$[\alpha]_D$.	Micro-m. p.	$[\alpha]_D$ ($\pm 2°$).
Alcohol	109·5° [1]	−11·9°	111—113°	−12°
Acetate	141 [1]	+22·4	146·5—147·5	+11
Benzoate	130 [1]	—	130—133	+29·5
Ketone	73—74 [3]	[+19·7 [4]]	82·5—84	−40·5
Dihydro-alcohol	Oil [2]	—	114—116	−14
Dihydro-acetate	119—120 [2]	+32·5	137—139	+13·5
Dihydro-benzoate	156 [2]	+48·1	138—139	+30·5
Dihydro-ketone	Oil [3]	—	80·5—81	−43

[1] Heilbron, Moffet, and Spring, *loc. cit.*
[2] Beynon, Heilbron, and Spring, *loc. cit.*
[3] Prepared from the corresponding alcohol by distillation from copper bronze powder (unpublished work).
[4] Recently determined on a surviving sample.

As has already been mentioned, the most striking reaction of basseol was its ready isomerisation to β-amyrin in the presence of acids. This behaviour is in no way paralleled by the new alcohol, and in no case has β-amyrin been detected in any reaction product from pure butyrospermol. The acetate of the latter can be crystallised unchanged from boiling acetic acid, but it is almost insoluble in formic acid, with which it forms an oil on heating, resolidifying unchanged on cooling. Butyrospermyl acetate, on standing at room temperature in solution in chloroform saturated with dry hydrogen chloride, is not recovered unchanged, but gives rise to a compound containing chlorine with a similar melting point to the original acetate but a higher positive specific rotation. This product has not yet been fully investigated. Basseol acetate under these conditions gave β-amyrin in up to 90% yield (Beynon, Heilbron, and Spring, *loc. cit.*).

While only preliminary degradation experiments have been carried out on butyrospermol, these indicate a further profound difference in structure from basseol. Ozonolysis of butyrospermyl acetate has given a 64% yield of acetone, estimated as its 2 : 4-dinitrophenylhydrazone, in contrast to the 20% yield of formaldehyde obtained from basseol (Beynon, Heilbron, and Spring, *loc. cit.*). No volatile fragment was produced on ozonolysis of dihydrobutyrospermyl acetate.

Butyrospermol is, therefore, probably a tetracyclic diethenoid secondary alcohol. Of the two double bonds, one is present in an *iso*propylidene group, and is very easily hydrogenated, the other is not readily hydrogenated but it reacts with perbenzoic acid. The empirical formula, $C_{30}H_{50}O$, suggests that it may be classed as a triterpene alcohol and it shows many similarities to euphol (Newbold and Spring, *J.*, 1944, 249).

Application of the method of molecular rotation differences (Barton and Jones, *J.*, 1944, 659) to butyrospermol and euphol and to their dihydro-derivatives reveals some similarity between these and agnosterol. It must be observed that in the absence of the ketone values, all the above could be associated with the lupeol–betulin group, but such an association is excluded in the case of butyrospermol.

TABLE II.

Substance.	M_D. Alcohol.	Acetate. (1)	Benzoate. (2)	Ketone. (3)	Δ_1.	Δ_2.	Δ_3.
α- and β-Amyrin group [1]	—	—	—	—	+ 6°	+145°	+ 60°
Lupeol–betulin group [1]	—	—	—	—	+ 70	+200	+140
Basseol [2]	− 51°	+ 94°	—	[+ 85° [3]]	+145	—	+136 [2]
Butyrospermol	− 51	+ 51	+180°	−170	+102	+231	−119
Dihydrobutyrospermol	− 60	+ 56	+164	−182	+116	+224	−122
Euphol [4]	+132	+211	[+329 [5]]	—	+ 79	[+197]	—
Dihydroeuphol [4]	+116	+165	—	—	+ 49	—	—
Agnosterol [1]	+301	+424	+549	—	+123	+248	—
Dihydroagnosterol [1]	+260	+393	—	—	+133	—	—

[1] Barton and Jones, *loc. cit.* [2] Heilbron *et al.*, *loc. cit.* [3] See Table I, footnote 4.
[4] Jeger and Krusi, *Helv. Chim. Acta*, 1947, **30**, 2047. [5] Rotation determined in pyridine solution.

It can be suggested, however, that for these compounds neither the ring carrying the hydroxyl group nor the adjacent ring contains a double bond, since no anomalous effects due to any possible vicinal action are observable. A second point that emerges is the small and negative change in the molecular rotation that is observed on hydrogenation of the reducible double bond in butyrospermol, euphol, and agnosterol (Table III) as compared with the much larger differences in the lupeol–betulin group (Barton and Jones, *loc. cit.*).

TABLE III.

Substance.	M_D. Triterpene.	Dihydro-compound.	Δ.
Agnosterol	+301°	+260°	− 41°
,, acetate	+424	+393	− 31
Euphol	+132	+116	− 16
,, acetate	+211	+165	− 46
Butyrospermol	− 51	− 60	− 9
,, acetate	+ 51	+ 56	+ 5
,, benzoate	+180	+164	− 16
Basseol acetate	+ 94	+155	+ 61
Lupeol (mean value) [1]	—	—	−190

[1] Barton and Jones, *loc. cit.*

Sample B of the shea nut fat has as yet only been saponified in small batches. The total yield of non-saponifiable matter was of the order of 3% of which more than half was rubbery material, insoluble in boiling acetic anhydride. A small quantity of butyrospermyl acetate was obtained by crystallisation of the mixed acetates.

Two independent samples of shea nut fat have thus been found to contain the new alcohol, butyrospermol, in place of the basseol isolated hitherto. [Bauer and Moll (*Fette und Seifen*, 1939, **46**, 560) claim to have isolated basseol during an investigation of the non-saponifiable matter of shea nut fat, but since no detailed examination of its properties was made it is possible that this material was impure butyrospermol.] At present no explanation can be offered to account for the absence of basseol and the presence of butyrospermol, but it is hoped that investigation of a series of samples of shea nut fat obtained from kernels of varying states of maturity and from different geographical areas may bring to light some new facts, possibly the existence of more than one species at present classed under the common name of *Butyrospermum parkii*, as is maintained by some botanical authorities (Dalziel, " The Useful Plants of Tropical West Africa ", p. 350; A. Chevalier, Pierre MS.; Yates, *Herb. Kewensis*).

Investigations have been made (*Bull. Imp. Institute*, 1930, **28**, 130; 1931, **29**, 417; 1932, **30**, 282; 1933, **31**, 334; 1935, **33**, 271; 1936, **34**, 437) into the seasonal and geographical variations in shea nut fat, primarily with regard to its superficial properties, such as iodine value, saponification value, percentage of non-saponifiable matter, etc., in an attempt to correlate these variations with some botanical feature. No correlation has been possible as a result of this work, large variations in properties being found in fat obtained from kernels from the same tree in different seasons, or from kernels from different trees with the same superficial botanical features. Two facts, however, have emerged from these investigations. First, that trees from the eastern (Sudanese) end of the geographical range of the shea tree yield a fat with a lower non-saponifiable content than that from the trees from the western regions; secondly, that as the kernel ripens, the percentage of non-saponifiable matter decreases, but that the absolute quantity in a kernel remains constant during its development.

Experimental

(All rotations are in chloroform in a 1 dcm. tube. All melting points are on the Kofler block and corrected unless specifically stated.)

Isolation of Butyrospermol from the Non-saponifiable Matter of Shea Nut Fat.—(a) *From sample A.* The non-saponifiable matter (1·4 kg.) was heated under reflux for 4 hours with acetic anhydride (7 kg.). The hot solution was decanted from a small quantity of insoluble grey sludge and allowed to cool overnight to room temperature, when a massive crop of sticky solid separated. This was filtered off, pressed free of acetic anhydride, and washed well with water (wt. after drying in a vacuum, 540 g.). The filtrate was cooled to below 0° for two days; a further crop of sticky brown solid had then separated. This was filtered off, washed with a little cold ethanol, and dissolved in hot ethyl acetate (250 c.c.), and the solution cooled, whereupon a mass of white needles separated. After being filtered and washed with alcohol, the acetate (48 g.) had m. p. 136—139° (capillary, uncorr.), $[\alpha]_D^{18°}$ +22·5° (*c*, 1·95). In the Liebermann–Burchard test it gave a brown colour with strong green fluorescence. On the Kofler micro-melting point block the substance had m. p. 138·5—147·5°, with crystals persisting in the melt to 180° or higher. The acetate (10 g.), after five crystallisations from ethanol–ethyl acetate (10 : 3), gave pure *butyrospermyl acetate* (2·2 g.), m. p. 146·5—147·5°, $[\alpha]_D^{20°}$ +11° ±2° (*c*, 2·58). The compound gave a brown colour with tetranitromethane, while in the Liebermann–Burchard test it gave a pale brown colour with strong green fluorescence. For analysis a sample was sublimed in a high vacuum at 160° (Found: C, 81·75; H, 11·05. $C_{32}H_{52}O_2$ requires C, 82·0; H, 11·2%). Chromatography of the impure acetate, $[\alpha]_D^{18°}$ +22·5°, (2 g.) on a column of Peter Spence alumina (130 g.), followed by elution with benzene–light petroleum (b. p. 40—60°) (1 : 4), gave the following fractions (each 100 c.c.):

Fraction.	Wt. (mg.).	M. p.	$[\alpha]_D^{19°}$.	Fraction.	Wt. (mg.).	M. p.	$[\alpha]_D^{19°}$.
1	trace	—	—	7	110	137—190°	+22·5°
2	60	up to 140°	—	8	100	137—190	—
3	230	138—143	+11°	9	90	136—150	—
4	220	135—141	+16	10	80	137—150	—
5	160	135—141	+22	11	60	138—230	+26
6	130	134—141	—				

Fraction 3 proved to be essentially butyrospermyl acetate, while Fraction 4 after crystallisation also gave the pure acetate.

(b) *From sample B.* The non-saponifiable matter (19·2 g.) was heated under reflux with acetic anhydride (100 c.c.) for 5 hours. The hot solution was decanted from a sticky residue (10·8 g.), and cooled to below 0° for two days. The separated solid was filtered off, washed with a little methanol, and dissolved in hot ethyl acetate (60 c.c.) and ethanol (100 c.c.). On cooling to room temperature a crop of solid (3·5 g.), m. p. up to 185°, separated. This was rejected. Evaporation of the mother-liquors gave a second crop (1·05 g.), which on recrystallisation from ethyl acetate gave a small quantity of β-amyrenyl acetate, m. p. 234—239°, and a third crop (1·3 g.), which on crystallisation from ethyl acetate gave almost pure butyrospermyl acetate, m. p. 143—145°, $[\alpha]_D^{19°}$ +16°.

Butyrospermol and Butyrospermyl Benzoate.—Butyrospermyl acetate (0·4 g.) was hydrolysed by heating under reflux with 5% alcoholic potassium hydroxide (20 c.c.) for 2 hours, the reaction mixture was poured into water, and the product was isolated with ether. Crystallisation from aqueous methanol gave *butyrospermol* as fine needles, m. p. 111—113°, $[\alpha]_D^{19°}$ −12° (*c*, 1·77). For analysis a specimen was dried for 5 hours at 80°/0·5 mm. (Found: C, 84·35; H, 11·7. $C_{30}H_{50}O$ requires C, 84·45; H, 11·8%). Benzoylation in pyridine at room temperature gave *butyrospermyl benzoate*, which crystallised from benzene–ethanol as leaflets, m. p. 130—133°, $[\alpha]_D^{19°}$ +33·5° (*c*, 1·64). The analytical sample was dried for 5 hours at 80°/0·5 mm. (Found: C, 83·5; H, 10·0. $C_{37}H_{54}O_2$ requires C, 83·7; H, 10·25%).

Perbenzoic Acid Titration of Butyrospermyl Acetate.—The acetate (98·2 mg.) was kept at 0° in a chloroform solution of perbenzoic acid (25 c.c., 0·25N) for 3 days. Titration of an aliquot part with 0·1N-thiosulphate solution showed that 1·71 atoms of oxygen had been absorbed. After a further 2 days, 2·03 atoms and after a total of 12 days 2·11 atoms of oxygen had been absorbed.

Butyrospermone.—(a) *By chromium trioxide oxidation of butyrospermol.* The alcohol (0·3 g.) in benzene (10 c.c.) was shaken at room temperature for 2·5 hours with a solution of chromium trioxide (0·1 g.) in "AnalaR" acetic acid (5 c.c.) and water (5 c.c.). The product, isolated with ether, failed to solidify and was chromatographed on Peter Spence alumina (30 g.). Elution with benzene–light petroleum (b. p. 40—60°) (1 : 9) gave *butyrospermone* (267 mg.) crystallising from methanol–chloroform as small prisms, m. p. 82·5—84°, $[\alpha]_D^{19°}$ −40° (*c*, 1·51). An analytical sample was dried at 60°/1 mm. for 8 hours (Found: C, 84·9; H, 11·3. $C_{30}H_{48}O$ requires C, 84·8; H, 11·4%).

(b) *By Oppenauer oxidation of butyrospermol.* Butyrospermol (275 mg.), *p*-benzoquinone (800 mg.), and aluminium *tert.*-butoxide (300 mg.) were heated under reflux in dry benzene (25 c.c.) overnight. The reaction mixture was steam distilled until free from benzoquinone, and the residue extracted with ether. The ethereal layer was washed with dilute sodium hydroxide in brine and then with water. Evaporation gave an oily residue (153 mg.) which was chromatographed on a column of Peter Spence alumina (30 g.). Elution with benzene–light petroleum (b. p. 40—60°) (1 : 19) gave butyrospermone (123 mg.), crystallising from methanol–chloroform as prisms, m. p. 82—84°, $[\alpha]_D^{19°}$ −43·5° (*c*, 1·20), identical with that obtained in (a).

Dihydrobutyrospermol.—Butyrospermol (4 g.) in ethanol (50 c.c.) together with a palladium on calcium carbonate catalyst (0·5 g.; 10%) was shaken in hydrogen at atmospheric temperature and pressure. Hydrogen (231 c.c.) was rapidly taken up, absorption ceasing abruptly at this stage (theoretical volume for one double bond = 235 c.c.). After removal of the catalyst by filtration, the ethanol solution was evaporated to a small bulk; *dihydrobutyrospermol* (3·8 g.) then crystallised as fine needles, m. p. 114—116° (depressed to 105—109° on admixture with butyrospermol), $[\alpha]_D^{19°}$ −14°

(*c*, 1·66). A sample for analysis was crystallised from methanol, and dried at 80°/1 mm. for 5 hours (Found: C, 83·6; H, 11·9. $C_{30}H_{52}O$ requires C, 84·05; H, 12·25%). Acetylation with acetic anhydride in pyridine gave the *dihydro-acetate* crystallising from ethanol–ethyl acetate in thick needles, m. p. 136—139° (undepressed on admixture with butyrospermyl acetate), $[\alpha]_D^{19°}$ +14° (*c*, 2·0), also obtained by hydrogenation of butyrospermyl acetate in ethyl acetate solution in presence of platinic oxide. With tetranitromethane it gave a pale yellow colour, while in the Liebermann–Burchard test it gave a yellow colour with pale green fluorescence. A sample for analysis was crystallised from ethanol, and dried at 100°/1 mm. for 5 hours (Found: C, 81·65; H, 11·45. $C_{32}H_{54}O_2$ requires C, 81·65; H, 11·6%). *Dihydrobutyrospermyl benzoate*, prepared by benzoylation of the alcohol in pyridine, crystallised from ethanol in long laths, m. p. 138—139°, $[\alpha]_D^{19°}$ +30·5° (*c*, 1·65). A sample for analysis was dried at 100°/1 mm. for 5 hours (Found: C, 83·1; H, 10·7. $C_{37}H_{56}O_2$ requires C, 83·4; H, 10·6%).

Dihydrobutyrospermone.—Dihydrobutyrospermol (1·0 g.) in benzene (5 c.c.) and "AnalaR" acetic acid (30 c.c.) was treated with chromium trioxide (0·2 g.) in water (1 c.c.). After being left overnight at room temperature, the product was isolated with ether. *Dihydrobutyrospermone* (1 g.) crystallised from ethanol in needles, m. p. 80·5—81°, $[\alpha]_D^{19°}$ −43° (*c*, 1·30). A sample for analysis was dried at 60°/1 mm. for 4 hours (Found: C, 84·9; H, 11·85. $C_{30}H_{50}O$ requires C, 84·45; H, 11·8%).

Reduction of Dihydrobutyrospermone.—Dihydrobutyrospermone (100 mg.) in ethanol (25 c.c.) was treated with sodium (2 g.) and the reaction allowed to proceed vigorously under reflux, solution of the last traces of sodium being effected by warming. After being poured into much water the product was extracted with light petroleum (b. p. 40—60°). The residue obtained by evaporation of the solvent was acetylated at room temperature in pyridine solution, and the product isolated by evaporation of the pyridine in a vacuum. Two crystallisations from ethanol gave dihydrobutyrospermyl acetate (60 mg.), m. p. 136—138° (undepressed on admixture with that previously obtained), $[\alpha]_D^{21°}$ +10° (*c*, 1·34).

Ozonolysis of Butyrospermyl Acetate.—Butyrospermyl acetate (2·0 g.) in carbon tetrachloride (30 c.c.) was treated with ozonised oxygen at 0° for 45 minutes (equivalent to 3 mols. of ozone). The carbon tetrachloride solution was evaporated to dryness in a vacuum, the residue dissolved in "AnalaR" acetic acid (30 c.c.), diluted with water (100 c.c.), and steam distilled until 100 c.c. of distillate had been collected. The distillate was treated with an excess of aqueous 2 : 4-dinitrophenylhydrazine sulphate solution and the voluminous yellow precipitate of acetone 2 : 4-dinitrophenylhydrazone filtered off and dried in a vacuum (wt. 0·65 g.; 64% yield). After one crystallisation from aqueous ethanol it had m. p. 124° (capillary, uncorr.) undepressed on admixture with an authentic sample.

The authors thank the Rockefeller Foundation for financial assistance. One of them (P. A. R.) is indebted to the Department of Scientific and Industrial Research for a Senior Research Award. Thanks are also expressed to the Director of the Colonial Products Research Council for his assistance in obtaining supplies of shea nut fat and to members of the staff of the Imperial Institute for their helpful advice.

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[*Received, May 13th*, 1948.]

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103. *Amidines. Part XI. Preparation of Amidines by Ammonolysis of* N-*Arylamidinium Salts.*

By P. OXLEY and W. F. SHORT.

N-Arylamidinium sulphonates, obtained from cyanides and arylammonium sulphonates at *ca.* 200°, afford good yields of unsubstituted amidinium sulphonates by ammonolysis at *ca.* 140°. This is a valuable method of preparation when poor yields are obtained directly from a cyanide and an ammonium sulphonate.

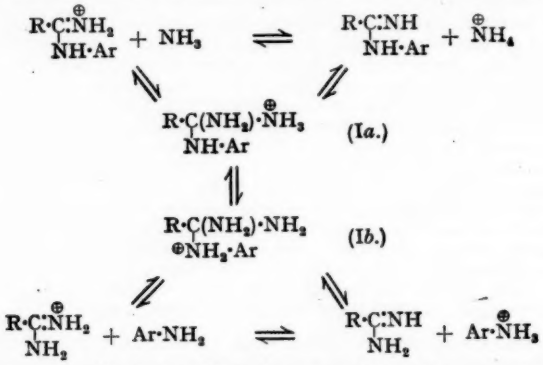
THIS communication describes the preparation of amidines in almost quantitative yield by heating *N*-arylamidinium salts in an atmosphere of ammonia at temperatures within the range 100—160°:

$$R{\cdot}C(NHAr){:}\overset{\oplus}{N}H_2 + NH_3 \longrightarrow R{\cdot}C(NH_2){:}\overset{\oplus}{N}H_2 + Ar{\cdot}NH_2$$

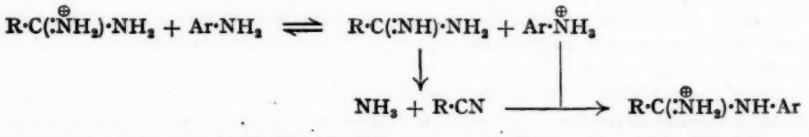
It is convenient to use the arylsulphonates of the *N*-arylamidines owing to the stability of the resulting unsubstituted amidinium salts and the relatively high solubility of both amidinium salts in the melt, but hydrochlorides, nitrates, acetates, and picrates have also been used. Some benzamidine (Fuller reaction) is produced by the slow ammonolysis of *N*-phenylbenzamidine in presence of phenol (1 mol.) at 140°, but the main product of the reaction is phenyl cyanide, produced by decomposition of the unsubstituted amidine. Aniline and nitrobenzene have been most frequently used as solvents in the ammonolysis of *N*-arylamidines, and although a number of other solvents has also been used (see Experimental section), alcohols seem to inhibit the reaction. It is often convenient to employ a mixture of an ammonium salt and an *N*-arylamidine in place of the reciprocal pair. The results obtained in the ammonolysis of a number of *N*-arylamidinium salts are collected in Table II, and it will be observed that high yields of unsubstituted amidinium salts are obtained at a comparatively low temperature. Since high yields of *N*-arylamidinium benzenesulphonates are almost invariably obtained from cyanides and arylammonium benzenesulphonates (see Table I) and this reaction takes place at a

considerably lower temperature than that required to convert a cyanide into an amidinium benzenesulphonate by the action of ammonium benzenesulphonate, ammonolysis of *N*-arylamidinium salts is a valuable method for the preparation of unsubstituted amidines, especially in cases where the cyanide undergoes some decomposition when strongly heated, or gives a low yield of amidinium salt with ammonium benzenesulphonate.

Ammonolysis of *N*-arylamidinium salts is surprisingly facile, and although most of the reactions were carried out at 140°, it was noted in several cases that a slow reaction occurs at a much lower temperature (see Table II). Thus, *N*-*p*-tolylphenylacetamidinium benzenesulphonate, which affords a 93% yield of the unsubstituted amidinium salt after an hour with ammonia at 140°, gives a 13% yield after 116 hours in liquid ammonia (−33°). Since there is no reaction between an *N*-arylamidine and ammonia or between an *N*-arylammonium salt and an ammonium salt at this temperature, we formulate the ammonolysis as follows :



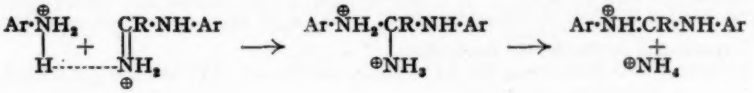
Decomposition of the unsubstituted amidine to a cyanide and ammonia is prevented by salt formation, and although it is probable that ammonolysis occurs by interaction between the arylamidinium ion and ammonia, the evidence does not exclude the possibility that the free arylamidine and the ammonium ion may be directly involved, and this alternative is therefore included in the scheme formulated above. The production of phenyl cyanide as main product of the interaction of *N*-phenylbenzamidine, ammonia, and phenol at 140° (above) indicates that, whilst phenol promotes ammonolysis of the substituted amidine, it is too weak an acid to prevent decomposition of the resulting benzamidine. Dissociation of the orthoamidinium ions to give the unsubstituted ion is probably promoted by the greater degree of resonance stabilisation of this ion, and since addition of a very large excess of arylamine to the reaction mixture does not appreciably affect the yield of unsubstituted amidine at temperatures up to 140°, the position of equilibrium in the reversible changes formulated above must be far on the side of the unsubstituted amidine. Moreover, no appreciable reaction between an arylamine and an unsubstituted amidinium salt could be detected up to 140°, and this recalls the observation that, whereas a number of cyanides combine with ammonia to give a small yield of amidine, yet they do not afford *N*-arylamidines with arylamines (Part VIII, *J.*, 1948, 303). If, however, an unsubstituted amidinium salt and an arylamine are heated at a higher temperature, ammonia is evolved and an *N*-arylamidinium salt is formed. The production of an *N*-arylamidinium salt under these conditions may also involve the formation of the orthoamidinium ions (I*a* and I*b*), the direction in which they dissociate at the high temperature being determined by the loss of ammonia from the system. It is also possible that the *N*-arylamidinium salt may be formed from an arylammonium salt and a cyanide produced by decomposition of the amidine (Part I; *J.*, 1946, 147) :



but the production of an *NN'*-diarylamidinium salt from an *N*-arylamidine and an arylammonium salt (see below) cannot be formulated in this way. At intermediate temperatures less ammonia will be lost from the system and the product will consist of an equilibrium mixture containing substantial proportions of both the arylamidinium and unsubstituted amidinium

salts, produced by arylation of the unsubstituted amidinium salt and ammonolysis of the *N*-arylamidinium salt respectively. Thus, *N*-phenylbenzamidinium benzenesulphonate dissolved in aniline affords an 88% yield of benzamidinium benzenesulphonate when heated at 100° for an hour in an atmosphere of ammonia, but at 185° an equilibrium mixture containing *ca.* 54% of benzamidine and *ca.* 27·5% of *N*-phenylbenzamidine (mainly as salts) is obtained whether one starts from benzamidinium benzenesulphonate and aniline (2 mols.), or from *N*-phenylbenzamidine, ammonium benzenesulphonate (1 mol.), aniline (1 mol.) and a trace of ammonia (equivalent to *N*-phenylbenzamidinium benzenesulphonate and a molecule of free ammonia). In either case, if the ammonia dissolved in the melt is displaced by a rapid stream of nitrogen, the product contains 23% of benzamidine, 46% of *N*-phenylbenzamidine, and 12% of *NN'*-diphenylbenzamidine. The effect of the concentration of the arylamine on the equilibrium is seen from the fact that, in contrast to the result obtained with 2 mols. of aniline, a mixture containing 74% of benzamidine and 14% of *N*-phenylbenzamidine is obtained at 185° from benzamidinium benzenesulphonate and 1 mol. of aniline, or from *N*-phenylbenzamidine and ammonium benzenesulphonate (1 mol.). The proportion of *N*-arylamidine at equilibrium appears to be determined by the basic strength of the arylamine. For example, the mixture obtained by heating *N*-*p*-chlorophenylbenzamidine, *p*-chloroaniline (1 mol.), and ammonium benzenesulphonate (1 mol.) at 185° contained only 6% of *N*-*p*-chlorophenylbenzamidinium benzenesulphonate, whereas the mixture obtained similarly from *N*-*p*-anisylbenzamidine, *p*-anisidine, and ammonium benzenesulphonate contained 39% of *N*-*p*-anisylbenzamidinium benzenesulphonate. It was therefore not surprising to find that *N*-alkylamidinium salts are more resistant to ammonolysis (see Table II) and that an *N*-phenyl-*N'*-methylbenzamidinium salt heated in ammonia at 140° yields as main product either an *N*-methylbenzamidinium salt or a benzamidinium salt according to the duration of the heating. *NN*- and *NN'*-Diarylamidinium salts undergo ammonolysis very readily, but *NNN'*-triphenylbenzamidinium benzenesulphonate is more resistant to ammonolysis than are the trialkylamidinium salts, and this may be due to the very weakly basic character of triphenylbenzamidine or to steric hindrance.

Bernthsen (*Annalen*, 1876, **184**, 354) observed that *NN'*-diarylamidinium chlorides are produced in addition to *N*-arylamidinium chlorides when methyl cyanide or phenyl cyanide is heated under pressure at 220—240° with phenyl- or *p*-tolyl-ammonium chloride (1 mol.), and sought to explain their formation on the basis of his observation that *NN'*-diphenylbenzamidinium chloride is produced by heating *N*-phenylbenzamidine and phenylammonium chloride (1 mol.) at 250°. The formation of *NN'*-diarylamidinium salts was not detected when a number of cyanides were heated with arylammonium benzenesulphonates (1 mol.) at 190—220° (Table I), but *NN'*-diphenylbenzamidinium benzenesulphonate is produced in 15% yield from phenyl cyanide and phenylammonium benzenesulphonate (1 mol.) at 270°, and *NN'*-di-*p*-tolylbenzamidinium benzenesulphonate is the main product (86%) of the interaction of phenyl cyanide with 2·5 mols. of *p*-tolylammonium benzenesulphonate at this temperature (Part I; *loc. cit.*). A mixture containing the benzenesulphonates of benzamidine (14%), *N*-phenylbenzamidine (53%), and *NN'*-diphenylbenzamidine (25%) is obtained either from *N*-phenylbenzamidine and phenylammonium benzenesulphonate (1 mol.) or from *NN'*-diphenylbenzamidine and ammonium benzenesulphonate (1 mol.) at 185°, and this is clearly the result of a balance between phenylation and ammonolytic reactions in equilibrium systems similar to those illustrated above. Contrary to Bernthsen's assumption, the production of *NN'*-diarylamidinium salts from an *N*-arylamidine and an arylammonium salt has no direct bearing on their production from cyanides and arylammonium salts, since in the latter case the intermediate *N*-arylamidine and the arylamine must both be present as salts. *N*-Phenylbenzamidinium benzenesulphonate and phenylammonium benzenesulphonate (1 mol.) do not react at 185°, but at 225° and 250° the product contains the benzenesulphonates of *N*-phenylbenzamidine (79 and 49%) and *NN'*-diphenylbenzamidine (12 and 37%). No benzamidine could be detected in the product at either temperature. These high-temperature reactions may involve dissociation of the arylammonium salt followed by reactions of the arylamine with the *N*-arylamidinium salt, or, less probably, the *NN'*-diarylamidinium salt may be formed by decomposition of a doubly charged orthoamidinium ion produced by combination of the *N*-arylamidinium and *N*-arylammonium ions:



Experimental.

Note.—Detailed descriptions of the isolation of the amidines are given only in special cases, since the methods employed followed closely those described in previous parts of this series, to which reference is made for earlier descriptions of some of the amidines (Part I, Oxley and Short, *J.*, 1946, 149; Part II, Oxley, Partridge, Robson, and Short, *ibid.*, p. 763; Part III, Oxley and Short, *J.*, 1947, 382; Part IV, Partridge and Short, *ibid.*, p. 390; Part VII, Oxley, Partridge, and Short, *ibid.*, p. 1110; Part VIII, Oxley, Partridge, and Short, *J.*, 1948, 303; Part IX, Oxley and Short, *ibid.*, p. 1514).

Preparation of N-*Substituted Amidines.*—Most of the *N*-substituted amidines used in the ammonolysis experiments were prepared by heating a cyanide with an equivalent of a *N*-arylammonium benzenesulphonate or toluene-*p*-sulphonate, following the methods described in Part I (*loc. cit.*). These experiments were conducted with 0·1—0·025 g.-mol. of cyanide, and the results are collected in Table I. Four amidines were prepared by the aluminium chloride method (Part VII) as described below, and the remainder were obtained by the methods indicated in the notes to Table II.

N-*Phenylbenzamidine.*—The temperature rose to 200° when powdered aluminium chloride (13·4 g.; 1 mol.) was added to a mixture of phenyl cyanide (10·3 g.) and aniline (9·3 g.; 1 mol.). The product was dissolved in water, and after the solution had been made alkaline with aqueous sodium hydroxide the amidine was collected in benzene. Concentration of the benzene solution afforded colourless crystals of *N*-phenylbenzamidine (15·3 g.; 78%) which had m. p. 116°, undepressed by admixture with specimens produced by other methods (Parts I, VII, and IX). *N*-Phenylbenzamidinium picrate had m. p. 148·5°, undepressed by admixture with an authentic specimen (Part IX).

N-cyclo*Hexylbenzamidine.*—Powdered aluminium chloride (13·4 g.; 1 mol.) was added to a mixture of phenyl cyanide (10·3 g.) and *cyclo*hexylamine (9·9 g.; 1 mol.). The temperature rose to 225°, and a solution of the product in hot water deposited colourless needles of N-cyclo*hexylbenzamidinium chloride*, m. p. 282° (yield 18·8 g., 79%) (Found: N, 11·5. $C_{13}H_{19}N_2Cl$ requires N, 11·7%). N-cyclo*Hexylbenzamidine* separated from light petroleum (b. p. 80—100°) in plates, m. p. 116—116·5° (Found: N, 13·8. $C_{13}H_{18}N_2$ requires N, 13·9%), and afforded a *picrate*, m. p. 143° (Found: N, 16·3. $C_{19}H_{21}O_7N_5$ requires N, 16·2%).

1 : 3-*Bis*-(p-*phenylamidinophenoxy*)*propane.**—Powdered aluminium chloride (2·67 g.; 1 mol.) was added during 10 minutes to a mixture of 1 : 3-bis-(*p*-cyanophenoxy)propane (5·56 g.) and aniline (3·72 g.; 2 mols.) previously heated to 140°. The temperature rose to 170° and, after being heated at 140° for 20 minutes, the mixture was cooled and decomposed with water (20 c.c.). The crude amidine (6·4 g.; 69%), m. p. 200—203°, was liberated with aqueous sodium hydroxide and had m. p. 206—207° after crystallisation from aqueous 2-ethoxyethanol. The amidine and its hydrochloride did not depress the m. p.s of specimens prepared by the alternative method (Table I, No. 22).

NN-*Diphenylbenzamidine.*—There was a 50° rise in temperature when aluminium chloride (13·4 g.; 1 mol.) was dissolved in a mixture of phenyl cyanide (10·3 g.) and diphenylamine (16·9 g.; 1 mol.). After being heated at 140° for an hour, the mixture was poured into water and extracted with benzene to remove unchanged cyanide and amine. The aqueous solution on being made alkaline with sodium hydroxide afforded *NN*-diphenylbenzamidine (2·5 g., 9%), m. p. 113°, undepressed by admixture with an authentic specimen (Part I). NN-*Diphenylbenzamidinium picrate* had m. p. 227° (Found: N, 14·2. $C_{25}H_{19}O_7N_5$ requires N, 14·0%).

Ammonolysis of N-*Substituted Amidines.*†—In order to avoid repetition, the results are collected in Table II. The description of the usual procedure which follows is supplemented where necessary by notes to the table. It is to be understood that identification of known compounds included not only the determination of the m. p. as quoted, but also comparison with an authentic specimen. Table III contains new salts of unsubstituted amidines prepared by ammonolysis of the *N*-substituted amidines.

The *N*-substituted amidinium salt (or a mixture of the amidine with an equivalent of an ammonium or substituted ammonium salt) was heated at *ca.* 140° (see Table II) with sufficient solvent to produce a homogeneous solution, which was kept saturated with ammonia by introducing a stream of fine bubbles of the gas from a capillary tube. Ammonia was frequently completely absorbed at the beginning of the experiment, and crystals of ammonium benzene- or toluene-*p*-sulphonate separated when nitrobenzene was used as solvent. This precipitate dissolved during the course of the experiment and the unsubstituted amidinium salt usually separated at a later stage or on cooling. More soluble amidinium salts were precipitated by adding acetone or ether. The method gave very clean products, so that one crystallisation from water or alcohol afforded the pure amidinium salt. The scale of the operations recorded in Table II was 0·002—0·02 g.-mol.

N-*Phenylbenzamidine and* cyclo*Hexylammonium Chloride.*—A solution of *N*-phenylbenzamidine (3·92 g.) and *cyclo*hexylammonium chloride (2·71 g.; 1 mol.) in aniline (5 c.c.) was heated at 140° for 2 hours, cooled, and diluted with ether (10 c.c.). The precipitate (3·38 g.), m. p. *ca.* 180°, consisted of a mixture of *N*-phenyl- and *N-cyclo*hexyl-benzamidinium chloride, and crystallisation from water afforded the less soluble *cyclo*hexylbenzamidinium chloride (1·52 g.; 32%) as flat needles, m. p. and mixed m. p. 282°.

Equilibrium between Reactions leading to the Ammonolysis of N-*Arylamidinium Salts and to the Arylation of Amidinium Salts at* 185°.—(A) *Systems containing benzamidine and* N-*arylbenzamidine.* (1) A mixture of *N*-phenylbenzamidine (1·96 g.) and ammonium benzenesulphonate (1·75 g.; 1 mol.) was heated at 185° for an hour, a slow stream of ammonia being passed into the mixture through a capillary tube. The product was cooled, diluted with acetone (10 c.c.), and cooled to 0°, whereupon it deposited benzamidinium benzenesulphonate (2·06 g.; 74%), m. p. and mixed m. p. 177°. The solvent was removed from the filtrate, which was then shaken with 2N-sodium hydroxide and benzene. The benzene solution was extracted with 10 × 5 c.c. of a 0·1N-sodium acetate–acetic acid buffer (pH 4·6), and the united extracts afforded *N*-phenylbenzamidine (0·27 g.; 13·8%), m. p. and mixed m. p. 115—116°, when

* Experiment by Dr. M. W. Partridge.

† See also Boots Pure Drug Co. Ltd., Oxley and Short, B.P. 612,980 (12.6.1946).

TABLE I.

Preparation of N-*arylamidines.*

	Reaction.			Base.			
N-Arylamidine.	Temp.	Time (hrs.).	Yield (%).	M. p.	Formula.	Found, N (%).	Calc. or reqd., N (%).
(1) N-p-*Tolyl*-n-*valeramidine*	190°	5	74	70°	$C_{12}H_{16}N_2$	14·8	14·7
(2) *N*-*p*-Tolylphenylacetamidine	220	1	84	—	—	—	—
(3) *N*-Phenyl-*p*-nitrophenylacetamidine	190	2½	65	—	—	—	—
(4) *NN'*-Diphenylmalonamidine	197	¾	51	—	—	—	—
(5) N-*Phenylamidino*cyclo*hexane*	190	2	81	129	$C_{13}H_{18}N_2$	13·95	13·9
(6) N-*Phenyl*-1-*amidino*cyclo*hexene*	190	5	90	88·5	$C_{13}H_{16}N_2$	14·0	14·0
(7) *N*-*o*-Chlorophenylbenzamidine	190	4	87	116	—	—	—
(8) *N*-*p*-Chlorophenylbenzamidine	190	4	90	117	—	—	—
(9) N-p-*Bromophenylbenzamidine*	220	½	64	121·5	$C_{13}H_{11}N_2Br$	10·4	10·2
(10) N-p-*Anisylbenzamidine*	210	2	58	115·5	$C_{14}H_{14}ON_2$	12·6	12·4
(11) N-*Phenyl*-o-*chlorobenzamidine*	190	5	56	100	$C_{13}H_{11}N_2Cl$	12·1	12·15
(12) *N*-Phenyl-2 : 4-dichlorobenzamidine	190	4½	64	102	$C_{13}H_{10}N_2Cl_2$	10·6	10·6
(13) *N*-Phenyl-*p*-methylsulphonylbenzamidine	175—180	3	86·5	—	—	—	—
(14) N-*Phenyl*-p-*ethylsulphonylbenzamidine*	190	2	97	195	$C_{15}H_{16}O_2N_2S$	9·8	9·7
(15) N-*Phenyl*-p-*sulphonamidobenzamidine*	190	2½	69	226—227 *	$C_{13}H_{13}O_2N_3S$	15·3	15·3
(16) *N*-Phenyl-*p*-toluamidine	190	6	81	152·5	$C_{14}H_{14}N_2$	13·4	13·3
(17) N-p-*Tolyl*-p-*toluamidine*	190	6	84	115	$C_{15}H_{16}N_2$	12·5	12·5
(18) N-p-*Chlorophenyl*-p-*toluamidine*	190	6	94	144·5	$C_{14}H_{13}N_2Cl$	11·5	11·5
(19) *N*-*p*-Tolyl-*p*-anisamidine	200	1	90	—	—	—	—
(20) *N*-Phenylveratramidine	200	2	73	—	—	—	—
(21) 1 : 2-Bis-(*p*-phenylamidinophenoxy)ethane	210	1	92	—	—	—	—
(22) 1 : 3-*Bis*-(p-*phenylamidinophenoxy*)*propane*	210—215	¼	97	206—207	$C_{29}H_{28}O_2N_4$	12·1	12·1
(23) *N*-Phenyl-1-naphthamidine	220	¾	69	—	—	—	—
(24) N-o-*Tolyl*-2-*naphthamidine*	210	1½	92	158	$C_{18}H_{16}N_2$	10·8	10·8
(25) N-*Phenylnicotinamidine*	190	4	93	135	$C_{12}H_{11}N_3$	21·1	21·3
(26) N-*Phenyl*-1-*naphthylacetamidine*	190	2	76	115—116	$C_{18}H_{16}N_2$	10·75	10·8

	Picrate.				Benzenesulphonate.			
	M. p.	Formula.	Found, N (%).	Calc. or reqd., N (%).	M. p.	Formula.	Found, N (%).	Calc. or reqd., N (%)
(1)	111°	$C_{18}H_{21}O_7N_5$	16·8	16·7	—	—	—	—
(2)	—	—	—	—	158°	$C_{22}H_{24}O_3N_2S$ †	6·9	7·1
(3)	—	—	—	—	163	$C_{20}H_{18}O_4N_2S$	10·1	10·2
(4)	—	—	—	—	206	$C_{27}H_{28}O_6N_4S_2$	9·7	9·9
(5)	164	$C_{19}H_{21}O_7N_5$	16·2	16·2	—	—	—	—
(6)	165·5	$C_{19}H_{19}O_7N_5$	16·3	16·3	—	—	—	—
(7)	199	—	—	—	—	—	—	—
(8)	183	—	—	—	217	$C_{19}H_{17}O_3N_2ClS$	7·4	7·3
(9)	181	$C_{19}H_{16}O_7N_5Br$	13·8	13·9	227	$C_{19}H_{17}O_3N_2BrS$	6·6	6·5
(10)	174·5	$C_{20}H_{17}O_8N_5$	15·6	15·4	159	$C_{20}H_{20}O_4N_2S$	7·4	7·3
(11)	165	$C_{19}H_{16}O_7N_5Cl$	15·0	15·2	—	—	—	—
(12)	156·5	$C_{19}H_{15}O_7N_5Cl_2$	13·9	14·2	183—183·5	$C_{19}H_{16}O_3N_2Cl_2S$	6·4; 6·5	6·6
(13)	—	—	—	—	—	—	—	—
(14)	—	—	—	—	—	—	—	—
(15)	—	—	—	—	235	$C_{19}H_{19}O_6N_3S_2$	9·8	9·7
(16)	153	$C_{20}H_{17}O_7N_5$	15·9	15·9	—	—	—	—
(17)	182·5	$C_{21}H_{19}O_7N_5$	15·55	15·45	184	$C_{21}H_{22}O_3N_2S$	7·5	7·3
(18)	192	$C_{20}H_{16}O_7N_5Cl$	15·0	14·8	252	$C_{20}H_{19}O_3N_2ClS$	6·9	7·0
(19)	—	—	—	—	221·5	$C_{22}H_{24}O_4N_2S$ †	6·8	6·8
(20)	—	—	—	—	177	$C_{21}H_{22}O_4N_2S$	6·9	6·8
(21)	—	—	—	—	250	$C_{40}H_{38}O_6N_4S_2$	7·2; 7·3	8·0
(22)	—	—	—	—	218—219	$C_{41}H_{40}O_6N_4S_2$	7·3	7·2
(23)	—	—	—	—	186	$C_{22}H_{20}O_3N_2S$	6·9	6·9
(24)	191	$C_{24}H_{19}O_7N_5$	14·45	14·3	178	$C_{24}H_{22}O_3N_2S$	6·6	6·7
(25)	—	—	—	—	—	—	—	—
(26)	164·5	$C_{24}H_{19}O_7N_5$	14·4	14·3	—	—	—	—

* With decomposition.

† Toluene-*p*-sulphonate.

Notes to Table I.—(1) p-*Tolyl*-n-*valeramidinium chloride* had m. p. 127—128° (Found: N, 12·4. $C_{13}H_{19}N_2Cl$ requires N, 12·4%). (6) The *hydrochloride* had m. p. 196—198° (decomp.) (Found: N, 11·7. $C_{13}H_{17}N_2Cl$ requires N, 11·8%). (7) Walther and Grossmann (*J. pr. Chem.*, 1908, **78**, 491) state that the amidine and its picrate have m. p. 114—115° and 193—194°, respectively. (8) Walther (*ibid.*, 1903, **67**, 450) records m. p. 115—116° and 183° for *N*-*p*-chlorophenylbenzamidine and its picrate, respectively. (11) N-*Phenyl*-*o*-*chlorobenzamidinium chloride* had m. p. 147° (Found: N, 10·6. $C_{13}H_{12}N_2Cl_2$ requires N, 10·5%). (12) The m. p.s of the amidine and benzenesulphonate agree with those recorded in Part VIII. The m. p. of the picrate is given as 148—149° in Part VII. (13) The m. p.s agree with those recorded in Parts IV and VIII. N-*Phenyl*-p-*methylsulphonylbenzamidinium chloride* had m. p. 162° (Found: C, 54·2; H, 4·85. $C_{14}H_{15}O_2N_2ClS$ requires C, 54·3; H, 4·85%). (14) N-*Phenyl*-p-*ethylsulphonylbenzamidinium chloride* crystallised from water as a monohydrate, m. p. 225° (Found: N, 8·2; H_2O, 5·4. $C_{15}H_{17}O_2N_2ClS,H_2O$ requires N, 8·2; H_2O, 5·3%). (16) Lottermoser (*J. pr. Chem.*, 1896, **54**, 129) states that *N*-phenyl-*p*-toluamidine has m. p. 149°. (22) Preparation by Dr. M. W. Partridge. The yield quoted refers to the crude amidine, m. p. 180—185°. The *hydrochloride* had m. p. 287—288° (decomp.) (Found: N, 10·5. $C_{29}H_{30}O_3N_4Cl_2$ requires N, 10·4%). The amidine was also prepared by the aluminium chloride method (see below).

TABLE II.

Ammonolysis of N-*substituted amidines.*

N-Substituted amidine.	Salt.*	Solvent.	Temp.	Time (hrs.).	Yield of unsubstituted amidine, %.
(1) *N*-p-Tolyl-*n*-valeramidine	T	NH_2Ph	140°	2	96
(2) *N*-*p*-Tolylphenylacetamidine	T	NH_2Ph	140	2	93
	T	liq. NH_3	−33	116	13
(3) *N*-Phenyl-*p*-nitrophenylacetamidine	B	NH_2Ph	140	1	62
(4) *N*-Phenylamidino*cyclo*hexane	B	NHMePh	100	2	73
	B	$Ph{\cdot}NO_2$	140	1½	94
(5) *N*-Phenylbenzamidine	B	$Ph{\cdot}NO_2$	56	2	45
	B	NH_2Ph	100	1	88
	B	NH_2Ac	140	1	80
	B	None	140	1	91
	B	C_5H_5N	15	14 days	33
	B	C_5H_5N/NH_3	15	14 days	62
	B	$(CH_2{\cdot}OH)_2$	140	1	20
	T	$Ph{\cdot}NO_2$	140	1	95
	Chloride	NH_2Ph	140	1	50
	Acetate	NH_4OAc	100	½	61
(6) *N*-*o*-Chlorophenylbenzamidine	B	$Ph{\cdot}NO_2$	140	5	91·5
(7) *N*-*p*-Chlorophenylbenzamidine	Nitrate	C_5H_5N	100	2	92
(8) *N*-*p*-Bromophenylbenzamidine	B	C_5H_5N	100	2	91
(9) *N*-*p*-Anisylbenzamidine	B	C_5H_5N	15	6 days	11
(10) *N*-2-Pyridylbenzamidine	T	$2\text{-}NH_2{\cdot}C_5H_4N$	140	1½	85
(11) *N*-*p*-Nitrophenylbenzamidine	B	$Ph{\cdot}NO_2$	140	2	98
(12) *N*-*cyclo*Hexylbenzamidine	Picrate	NH_2Ph	135	2	17
(13) *N*-Phenyl-*o*-chlorobenzamidine	B	$Ph{\cdot}NO_2$	140	5	90
(14) *N*-Phenyl-2 : 4-dichlorobenzamidine	B	$Ph{\cdot}NO_2$	140	1	57·5
(15) *N*-Phenyl-*p*-methylsulphonylbenzamidine	B	NH_2Ph	140	1	93
(16) *N*-Ethyl-*p*-methylsulphonylbenzamidine	T	NH_2Ph	140	3	56
(17) *N*-*p*-Tolyl-*p*-toluamidine	B	NMe_2Ph	140	2	96
(18) *N*-*p*-Chlorophenyl-*p*-toluamidine	T	NHMePh	140	3	93
(19) *N*-*p*-Tolyl-*p*-anisamidine	T	NH_2Ph	140	2	98
(20) *N*-Phenylveratramidine	B	$Ph{\cdot}NO_2$	140	1	*ca.* 100
(21) 1 : 2-Bis-*p*-(phenylamidinophenoxy)-ethane	2B	NH_2Ph	140	1	95
(22) 1 : 3-Bis-(*p*-phenylamidinophenoxy)-propane	2B	NH_2Ph	110	6	70
(23) *N*-Phenyl-1-naphthamidine	B	NH_2Ph	140	5	94·5
(24) *N*-*o*-Tolyl-2-naphthamidine	B	$Ph{\cdot}NO_2$	140	3	93
(25) *N*-Phenylpicolinamidine	B	NH_2Ph	140	2	90
(26) *N*-Phenyl-*N'*-methylbenzamidine	B	NH_2Ph	140	1	32
(27) *N*-Phenyl-*N*-methylbenzamidine	T	$Ph{\cdot}NO_2$	140	3	98
	Picrate	NH_2Ph	140	2	60
(28) *NN'*-Diphenylbenzamidine	B	NH_2Ph	140	1	73
(29) *NN*-Diphenylbenzamidine	B	$Ph{\cdot}NO_2$	140	5	93·5
(30) *N*-Phenyl-*N'*-benzylbenzamidine	Picrate	NH_2Ph	140	1½	16
(31) *NN*-Diethyl-*p*-methylsulphonylbenz-amidine	T	Quinoline	100	1⅓	40
(32) *NNN'*-Triphenylbenzamidine	B	NH_2Ph	140	3	—
(33) *NN*-Pentamethylene-*N'*-phenylbenz-amidine	B	NH_2Ph	140	4½	36
(34) *N*-Methyl-*NN'*-diethylbenzamidine	B	None	135	4	17
(35) *N*-Phenyl-1-naphthylacetamidine	T	NH_2Ph	140	2	87

* B = Benzenesulphonate. T = Toluene-*p*-sulphonate.

Notes to Table II.—The preparation of a number of the *N*-substituted amidines is described in the previous section and the rest were obtained as described in earlier parts of this series as follows: Part I, No. 11; Part III, Nos. 26, 34; Part VII, Nos. 10, 16, 27, 28, 31; Part IX, Nos. 28, 30, 32, 33; Part X, No. 26. (1) *n*-Valeramidinium picrate had m. p. 195—196°, in agreement with Easson and Pyman (*J.*, 1931, 2991). (2) Phenylacetamidine and its salts are described in Parts I, IV, VII, and VIII. (5) In the first experiment using pyridine as solvent *N*-phenylbenzamidine was brought into reaction with ammonium benzenesulphonate (1 mol.); in the second experiment, the solution was also saturated with ammonia. When ammonia was passed for 2½ hours into an equimolecular mixture of *N*-phenylbenzamidine and phenol at 140°, the product contained 30% of unchanged amidine, and 48% of phenyl cyanide. The reaction mixture gave a colouration with Fuller's reagent throughout, indicating the presence of the unsubstituted amidine, but the amount was insufficient to allow benzamidine to be isolated. References to benzamidine and its salts are given in Parts I, IV, V, VII, and VIII. The benzenesulphonate had m. p. 178°, and the picrate m. p. 240°. (15) and (16) *p*-Methylsulphonylbenzamidine and its salts are described in Parts I, II, IV, and VII. (17 and (18) *p*-Toluamidine has been described by Glock (*Ber.*, 1888, **21**, 2651), Tiemann (*ibid.*, 1891, **24**, 371), Crayen (*ibid.*, p. 391), and Eitner (*ibid.*, 1893, **26**, 2839). (20) Veratramidinium picrate had m. p. 218°. Pyman and Easson (*loc. cit.*, p. 2995) give m. p. 217—218°. (21) References to the amidine and its salts are given in Part I. (22) Experiment by Dr. M. W. Partridge. For references see Parts I, IV, and VIII. (23) References to 1-naphthamidine are given in Part I. (24) References to 2-naphthamidine are given in Parts I, IV, and VII. (25) Crude *N*-phenylpicolinamidinium benzenesulphonate, obtained by heating 2-cyanopyridine (5·2 g.) and ammonium benzenesulphonate (12·55 g.; 1 mol.) at 200° for an hour, was mixed with aniline (10 c.c.) and heated at 140° for 2 hours in a stream of ammonia. The yield is calculated on the 2-cyanopyridine. Picolinamidine and its salts are described in Parts I and IV. (26) *N*-Methylbenzamidinium benzenesulphonate (64%), m. p. and mixed m. p. 129° (Part III), was obtained by adding ether to the aniline solution obtained as filtrate from the benzamidinium benzenesulphonate. (32) The presence of benzamidine in the product was indicated by the production of a colouration with Fuller's reagent, but the amount present was too small to isolate.

TABLE III.

Amidinium salts prepared by ammonolysis.

Amidine.	Salt.	M. p.	Formula.	Found, N (%).	Calc. or reqd., N (%).
(1) *n*-Valeramidine	*Toluene-p-sulphonate*	134°	$C_{12}H_{20}O_3N_2S$	10·2	10·3
(2) Phenylacetamidine	*Toluene-p-sulphonate*	199	$C_{15}H_{16}O_3N_2S$	9·1	9·15
(3) *p*-Nitrophenylacetamidine	*Benzenesulphonate*	198·5	$C_{14}H_{13}O_5N_3S$	12·6	12·5
(4) Amidino*cyclo*hexane	*Picrate*	230—232 *	$C_{13}H_{17}O_7N_5$	19·9	19·7
(5) Benzamidine	Acetate	243 *	$C_9H_{12}O_2N_2$	15·4	15·6
(6) 2-Chlorobenzamidine	*Benzenesulphonate*	167	$C_{13}H_{13}O_3N_2ClS$	9·0	9·0
(7)	*Picrate*	217	$C_{13}H_{10}O_7N_5Cl$	18·2	18·2
(8) 2 : 4-Dichlorobenzamidine	*Benzenesulphonate*	258	$C_{13}H_{12}O_3N_2Cl_2S$	8·1	8·1
(9)	*Picrate*	205	$C_{13}H_9O_7N_5Cl_2$	16·9	16·7
(10) *p*-Toluamidine	*Benzenesulphonate*	195·5	$C_{14}H_{16}O_3N_2S$	9·7	9·6
(11)	*Toluene-p-sulphonate*	191	$C_{15}H_{18}O_3N_2S$	9·4	9·2
(12)	Picrate	229	$C_{14}H_{13}O_7N_5$	19·4	19·3
(13) *p*Anisamidine	*Toluene-p-sulphonate*	206	$C_{15}H_{18}O_4N_2S$	8·8	8·7
(14) Veratramidine	*Benzenesulphonate*	190	$C_{15}H_{18}O_5N_2S$	8·3	8·3
(15) 1 : 3-Bis-(*p*-amidinophenoxy)ethane	Bisbenzenesulphonate	*ca.* 312	$C_{28}H_{30}O_6N_4S_2$	9·0	9·1
(16) 1-Naphthamidine	Benzenesulphonate	218	$C_{17}H_{16}O_3N_2S$	8·5	8·5
(17) 1-Naphthylacetamidine	*Toluene-p-sulphonate*	188	$C_{19}H_{20}O_3N_2S$	7·8	7·9
	Picrate	248—249 *	$C_{18}H_{15}O_7N_5$	16·7	16·9

* Compounds having m. p.s marked with an asterisk decompose on melting.

Notes to Table III.—(3) This amidinium salt gave a strong colouration with Fuller's reagent, which is usually considered to be specific for compounds containing an unsubstituted amidino-group joined directly to an aromatic nucleus (Fuller, *Nature*, 1944, **154**, 773; *Biochem. J.*, 1945, **39**, 99). (5) Pinner ("Imidoäther," 1892, p. 156) records m. p. 229° (decomp.). (6) 2-Chlorobenzamidinium benzenesulphonate, m. p. 167°, was also obtained in 6% yield by heating *o*-chlorophenyl cyanide and ammonium benzenesulphonate (1 mol.) at 240° for 2¾ hours. (12) The m. p. of the picrate is recorded as 224—225° by Ponzio and Zamardi-Lamberti (*Gazzetta*, 1923, **53**, 818) and as 219° (decomp.) by Kirsanov and Polyakova (*Bull. Soc. chim.*, 1936, **3**, 1600). (15) The m. p. is given as >270° in Part I. (16) The m. p. recorded in Part I is 211°.

made alkaline with aqueous sodium hydroxide. When the reaction mixture consisted of *N*-phenylbenzamidine (1·96 g.), ammonium benzenesulphonate (1·75 g.; 1 mol.), and aniline (0·93 g.; 1 mol.), the product afforded 1·49 g. (53·6%) of benzamidinium benzenesulphonate and 0·54 g. (27·6%) of *N*-phenylbenzamidine.

(2) When a mixture of benzamidinium benzenesulphonate (2·78 g.) and aniline (0·93 g.; 1 mol.) was heated at 185° for an hour, benzamidinium benzenesulphonate (1·97 g.; 71%) and *N*-phenylbenzamidine (0·28 g.; 14·3%) were isolated from the product as described in (1). When the quantity of aniline was increased to 1·86 g. (2 mols.) the amount of unchanged benzamidinium benzenesulphonate fell to 54% and the yield of *N*-phenylbenzamidine rose to 28%.

Similar experiments, each on a 0·01 g.-molar scale, were carried out with other *N*-arylbenzamidines, equimolecular quantities of the *N*-arylamidine, ammonium benzenesulphonate, and the arylamine being heated at 185° for an hour. The products, which were identified in each case by direct comparison with an authentic specimen, were separated by the method described in (1), and the results were as follows:

Ar.	*N*-Arylbenzamidine, HN:CPh·NH·Ar, %.	Benzamidinium benzenesulphonate, %.
Ph	28	54
$C_6H_4Cl(p)$	6	79
C_6H_4·OMe(*p*)	39	34

The effect of reducing the concentration of dissolved ammonia was seen in an experiment in which a rapid stream of nitrogen was passed into a mixture of benzamidinium benzenesulphonate (2·78 g.) and aniline (1·86 g.; 2 mols.) kept at 185° for an hour. Benzamidinium benzenesulphonate (23%), *N*-phenylbenzamidine (46·4%), and *NN'*-diphenylbenzamidinium chloride (11·7%), m. p. and mixed m. p. 302—304°, were isolated from the product. The disubstituted amidinium chloride separated when the benzene solution from which the *N*-phenylbenzamidine had been extracted with sodium acetate–acetic acid was shaken with 2N-hydrochloric acid.

(B) *The system containing* N-*phenylbenzamidine and* NN'-*diphenylbenzamidine.* A mixture of *NN'*-diphenylbenzamidine (2·72 g.) and ammonium benzenesulphonate (1·75 g.; 1 mol.) was heated at 185° for 2 hours, cooled, stirred with water (10 c.c.), and neutralised to Congo-red with benzenesulphonic acid. The precipitate consisted of *NN'*-diphenylbenzamidinium benzenesulphonate (1·09 g.; 25·3%), m. p. and mixed m. p. 213—215°. The filtrate was made alkaline with 5N-sodium hydroxide (5 c.c.), shaken with benzene (25 c.c.), and the aqueous solution (S) was separated. The benzene solution was extracted with sodium acetate–acetic acid buffer (pH 4·6; 10 × 5 c.c.) and *N*-phenylbenzamidine (1·04 g.; 53%), m. p. and mxed m. p. 114—115°, was obtained by adding sodium hydroxide to the separated aqueous layer. The solution (S) was neutralised with acetic acid and afforded benzamidinium picrate (0·49 g.; 14%), m. p. and mixed m. p. 337—338°, when mixed with aqueous ammonium picrate.

In the same way, *N*-phenylbenzamidine (1·96 g.) and phenylammonium benzenesulphonate (2·51 g.; 1 mol.), heated at 185° for 2 hours, afforded *NN'*-diphenylbenzamidinium benzenesulphonate (25%), *N*-phenylbenzamidine (45%), and benzamidinium picrate (12%).

Reaction between Amidinium Benzenesulphonates and Phenylammonium Benzenesulphonate.—The reaction products were separated in each case by employing the method described in the previous section.

(1) There was no visible change when benzamidinium benzenesulphonate (1·39 g.) and phenylammonium benzenesulphonate (1·255 g.; 1 mol.) were heated at 185° for an hour, and almost all the amidine was recovered. When the mixture was heated at 245°, phenyl cyanide was formed, and after an hour's heating 64% of the benzamidine was recovered and a 7% yield of *N*-phenylbenzamidine was obtained.

(2) *N*-Phenylbenzamidinium benzenesulphonate and ammonium benzenesulphonate did not appear to react at 185° and the product did not contain benzamidine after 2 hours' heating, since no colour reaction was obtained with Fuller's reagent. There was slight decomposition at 235° but the Fuller reaction was still negative. When the mixture was heated at 250—265° there was considerable decomposition with production of phenyl cyanide and a weak Fuller reaction was obtained.

(3) *N*-Phenylbenzamidinium benzenesulphonate (3·54 g.) and phenylammonium benzenesulphonate (2·51 g.; 1·0 mol.) did not react at 185°, the amidine being recovered almost quantitatively. After 2½ hours at 225°, the product contained *N*-phenylbenzamidine (79%), *NN'*-diphenylbenzamidine (12%), and phenyl cyanide (trace), but no benzamidine could be detected in it by means of Fuller's reagent. Similarly, after an hour at 250° the product contained *N*-phenylbenzamidine (49%), *NN'*-diphenylbenzamidine (37%), an appreciable amount of phenyl cyanide, but no benzamidine.

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[*Received, May 25th,* 1948.]

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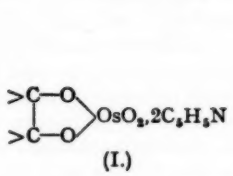
104. *The Relative Reactivity of Aromatic Double Bonds.*

By G. M. BADGER.

In the presence of pyridine, osmium tetroxide is added to certain reactive aromatic double bonds with the formation of brown complexes. A method for studying the rate of addition has been developed, and the reaction shown to be of the second order. The rate of addition to 18 carcinogenic and related non-carcinogenic hydrocarbons has been studied. The substitution of alkyl groups, especially in "favourable" positions, increases the rate of addition, while the cyano-group decreases it. These results are discussed in relation to theories of chemical constitution and carcinogenic activity.

CRIEGEE *et al.* (*Annalen*, 1936, **522**, 75; 1942, **550**, 99) observed that osmium tetroxide, in the presence of pyridine, reacts with compounds containing an ethylenic double bond with the formation of coloured complexes having the structure of osmic esters (I). This reaction has recently been extended to polycyclic aromatic hydrocarbons by Cook and Schoental (*J.*, 1948, 170; *Nature*, 1948, **161**, 237), who observed that, in every case, the addition was to adjacent carbon atoms. With anthracene, for example, addition to the 1 : 2- and 3 : 4-bonds took place,

and with 1 : 2-benzanthracene (II), addition to the 3 : 4-bond. This should be compared with the fact that most reagents which have been investigated give rise to *meso*-substitution or *meso*-addition products of anthracene and its derivatives. Again, with pyrene (III), the addition was to the 1 : 2-bond although most reagents oxidise, or substitute, this hydrocarbon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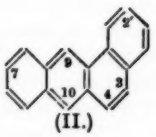
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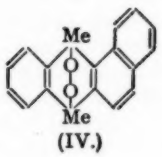
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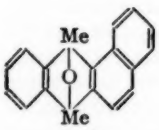
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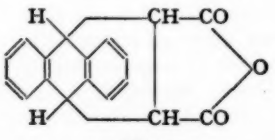
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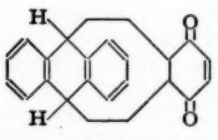
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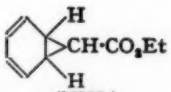

(VIII.)

at positions 3, 5, 8, and 10, to give 3 : 8- and 3 : 10-disubstituted, or 3 : 5 : 8 : 10-tetrasubstituted pyrenes. These facts favour the view that osmium tetroxide can only react as a " double bond " reagent, for there does not seem to be any theoretical objection to a transannular addition with anthracene and its derivatives. Anthracene is known to form a photo-oxide by the transannular addition of oxygen (Dufraise and Gérard, *Bull. Soc. chim.*, 1937, **4**, 2052). 9 : 10-Dimethyl-1 : 2-benzanthracene, and many other substituted anthracenes, are also known to form stable photo-oxides which have been shown to have the structure of *endo*-peroxides (IV) (Cook and Martin, *J.*, 1940, 1125). It is of some interest that a stable *endo*mono-oxide (V) has also been reported (Badger, Goulden, and Warren, *J.*, 1941, 18), having been prepared by transannular dehydration of 9 : 10-dimethyl-9 : 10-dihydroxy-9 : 10-dihydro-1 : 2-benzanthracene. Anthracene and its derivatives also form transannular adducts (VI and VII) with maleic anhydride and with *p*-benzoquinone (see Clar, " Aromatische Kohlenwasserstoffe ", 1941; also Bartlett, Ryan, and Cohen, *J. Amer. Chem. Soc.*, 1942, **64**, 2649).

Considerable interest attaches to the mechanism of the addition of osmium tetroxide to double bonds. The data available at present are few, but it seems to be important that osmium tetroxide reacts with aromatic hydrocarbons, and with compounds containing ethylenic double bonds, in a manner analogous to that of reagents such as ozone and diazoacetic ester. As has already been mentioned, the addition of osmium tetroxide to pyrene takes place at the 1 : 2-bond, and this is also the first bond to be attacked by ozone (Vollmann, Becker, Corell, and Streeck, *Annalen*, 1937, **531**, 1; Fieser and Novello, *J. Amer. Chem. Soc.*, 1940, **62**, 1855). This seems to indicate that the 1 : 2-bond is the most reactive *bond* in pyrene, although the 3, 5, 8, and 10 positions are the most reactive *centres* (compare Robertson and White, *J.*, 1947, 358; Moffitt and Coulson, *Proc. Physical Soc.*, 1948, **60**, 309). Ozone attacks anthracene, but the products do not seem to have been determined. With naphthalene and its derivatives, either a diozonide or a pentozonide is formed (Long, *Chem. Reviews*, 1940, **27**, 437; Harries, *Annalen*, 1905, **343**, 311; Wibaut and van Dijk, *Rec. Trav. chim.*, 1946, **65**, 413; Kooyman, *ibid.*, 1947, **66**, 201). As mentioned above, osmium tetroxide gives rise to anthracene-1 : 2-3 : 4-diosmate, and a similar result may be expected with naphthalene, although this has not yet been confirmed. Diazoacetic ester also attacks aromatic and ethylenic doubles bonds (Smith, *Chem. Reviews*, 1938, **23**, 193). The products are pyrazolines, which decompose with evolution of nitrogen to give norcaradiene derivatives (VIII). Some other diazo-compounds behave similarly (Fieser and Peters, *J. Amer. Chem. Soc.*, 1931, **53**, 4080).

The additions of these reagents to double bonds is therefore very similar. For the present purpose, however, the detailed mechanism is not important. The relative reactivities of two substances will be governed by two factors : (i) the relative polarisabilities of the double bonds, and (ii) the percentages of double-bond character. It seems unlikely that relative polarisability will exert an important effect, but, in any case, with closely related substances the polarisabilities may be assumed to be identical, and the relative rates of reaction with osmium tetroxide should be comparable with the density of π electrons, or with the double-bond character.

For preparative purposes (cf. Criegee *et al.*, *loc. cit.*; Cook and Schoental, *loc. cit.*), the reaction is usually carried out in a solvent such as benzene, in which the complexes are sparingly soluble.

The complexes are, however, soluble in methylene chloride, chloroform, etc., and these solvents were therefore indicated for kinetic work. A preliminary account of a comparison between the rate of addition of osmium tetroxide to 1 : 2-benzanthracene and to phenanthrene has already been published (Badger and Reed, *Nature*, **1948**, **161**, 238). In this case the reaction between the hydrocarbon and osmium tetroxide was carried out at 30°, in pure chloroform.

Pure chloroform, from which the alcohol has been removed, is notoriously unstable, giving rise to hydrogen chloride and carbonyl chloride, and in further experimental work difficulties were often encountered owing to the development of these decomposition products, and the apparent instability of the complex. An investigation into the stability of osmium tetroxide and of the complexes, in chloroform, was accordingly undertaken. Osmium tetroxide was found to be stable in solution in chloroform, for at least a week, so that standard solutions may safely be made up and used within that time. On the other hand, such solutions give rise to varying amounts of chloroform decomposition products within a few days. In chloroform B.P. (*i.e.*, pure anæsthesia chloroform containing alcohol) osmium tetroxide is unstable, and rapidly gives a black precipitate. The 1 : 2-benzanthracene-3 : 4-osmate–pyridine complex was found to be stable in pure chloroform for at least 24 hours, but unstable in chloroform containing decomposition products. On the other hand, the complex was found to be stable in chloroform containing decomposition products to which a little pyridine had been added. Hydrogen ions are evidently involved in the decomposition : this has been demonstrated by passing hydrogen chloride through a solution of the complex in pure chloroform. Criegee (*loc. cit.*) has previously observed that osmic esters are converted into " diesters " by treatment with acids.

In view of these results, it was decided to carry out the reaction in pure chloroform containing 4% of pyridine. A temperature of 20° was used. Colour intensities were measured at suitable intervals with a Spekker absorptiometer, using green filters, the instrument being calibrated with known concentrations of the appropriate complex. Green filters gave the most satisfactory results, reducing the effect of the yellow osmium tetroxide–pyridine solution to a minimum. A correction for the absorption of this solution was, however, applied. The reactions were followed for 24 hours.

According to Criegee (*loc. cit.*), pyridine and osmium tetroxide quickly interact to form a complex, OsO_4,C_5H_5N. The author has found, however, that the prolonged action of osmium tetroxide on pyridine gives rise to a highly crystalline, sparingly soluble, light brown *complex*, $OsO_4,2C_5H_5N$. This means that the use of pyridine in the hydrocarbon–osmium tetroxide reaction mixture must introduce an error which, although small for fast reactions, may be quite large with very slow reactions. For this reason the method is unsuitable for the accurate determination of slow reactions, and in the present work no rate constants have been calculated for those substances found to react substantially slower than benzanthracene (*i.e.*, those reactions less than 40% complete in 24 hours). The absolute accuracy of the present determinations may not be high, but for determinations of the reaction rates of two similar compounds the relative accuracy is probably about $\pm 5\%$.

With most of the compounds studied, a concentration of about 0·015 or 0·020M was found to give a satisfactory rate of reaction. Indeed, it has not been possible to study these compounds over as large a range of concentration as might be desired. The sparing solubility of most of the polycyclic aromatic compounds, and the intense yellow colour of the osmium tetroxide–pyridine solutions, prevents the study of high concentrations, while the slowness of the reaction and the side reaction with pyridine already mentioned make it difficult to follow the reaction at great dilutions. With these limitations the reaction with benzanthracene has been studied at five concentrations. Within experimental error, the same rate constant (in g.-mol.$^{-1}$ sec.$^{-1}$ l.) was obtained (see Table I). This indicates that the reaction is of the second order.

TABLE I.

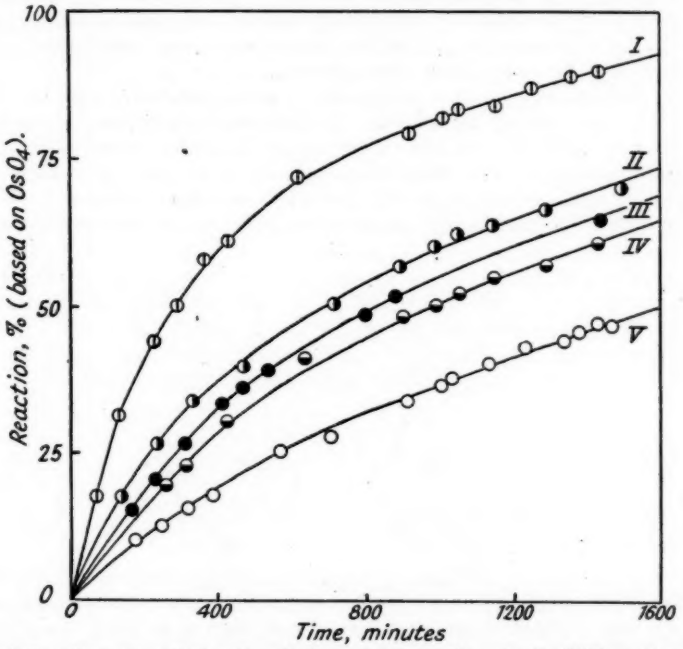
Reaction between 1 : 2-*benzanthracene and osmium tetroxide in* 4% *pyridine in chloroform, at* 20°.

1 : 2-Benzanthracene, M.	OsO_4, M.	10^4k_2.	1 : 2-Benzanthracene, M.	OsO_4, M.	10^4k_2.
0·02000	0·01542	$4·75\pm0·24$	0·03000	0·03064	$4·57\pm0·36$
0·02000	0·02145	$4·86\pm0·30$	0·03000	0·02208	$4·74\pm0·24$
0·02500	0·01766	$4·86\pm0·29$		Mean	4·76

It appeared to be desirable to confirm that the reaction follows the same course in solution in chloroform as has been demonstrated (Cook and Schoental, *loc. cit.*) for benzene solution. This was carried out by using the reaction mixture remaining unused after the above determinations with 1 : 2-benzanthracene. The mixture was hydrolysed to 3 : 4-dihydroxy-3 : 4-dihydro-

1 : 2-benzanthracene, and this was converted into the diacetyl derivative, shown to be identical with a specimen prepared by Dr. R. Schoental.

The rate of addition of osmium tetroxide to 18 carcinogenic and related non-carcinogenic polycyclic aromatic compounds has been studied under standard conditions: hydrocarbon, 0·020M; osmium tetroxide, 0·0154M. Attention was concentrated on derivatives of 1 : 2-benz-



Curves illustrating the effect of methyl and methylene group on the rate of addition of osmium tetroxide to 1 : 2*-benzanthracenes.* I, 9 : 10*-Dimethyl-*1 : 2*-benzanthracene.* II, *Methylcholanthrene.* III, 10*-Methyl-*1 : 2*-benzanthracene.* IV, 2′ : 7*-Dimethyl-*1 : 2*-benzanthracene.* V, 1 : 2*-Benzanthracene.*

anthracene, which may reasonably be assumed to have comparable polarisabilities, although examples of other types of carcinogen have been examined. The results clearly show (see figure) that alkyl groups act as electron donors to the ring, and increase the density of π electrons at the point of addition. This is reflected in the increased reactivity towards osmium tetroxide. The effect varies in magnitude with the position of the alkyl group, and is at a maximum when

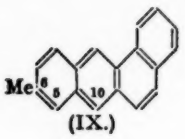
TABLE II.

Rates of reaction of osmium tetroxide and carcinogenic compounds, in 4% pyridine in chloroform, at 20°. (k_2 *in* g.-mol.$^{-1}$ sec.$^{-1}$ l.)

Compound.	10^3k_2.	Carcinogenic activity.
5 : 6 : 9 : 10-Tetramethyl-1 : 2-benzanthracene	2·9	+++
9 : 10-Dimethyl-1 : 2-benzanthracene	2·7	++++
9 : 10-Diethyl-1 : 2-benzanthracene	2·1	+++
20-Methylcholanthrene	1·1	++++
Acenaphthanthracene	1·1	+
Cholanthrene	1·0	++++
3 : 4-Benzpyrene	0·94	++++
10-Methyl-1 : 2-benzanthracene	0·91	+++
1 : 2-Dimethylchrysene	0·84	++
2′ : 7-Dimethyl-1 : 2-benzanthracene	0·83	0
5 : 6-Dimethyl-1 : 2-benzanthracene	0·64	++
6-Methyl-1 : 2-benzanthracene	0·64	+
1 : 2 : 5 : 6-Dibenzanthracene	0·64	++
1 : 2-Benzanthracene	0·48	0
10-Cyano-9-methyl-1 : 2-benzanthracene	0·40	++++
10-Cyano-1 : 2-benzanthracene	very slow	+
6-Methyl-3 : 4-benzphenanthrene	,,	+
1 : 2 : 5 : 6-Dibenzphenanthrene	,,	+

the group or groups are in the *meso*-positions (*e.g.*, 10-methyl-, 9 : 10-dimethyl-, and 9 : 10-diethyl-1 : 2-benzanthracene; see also Table II). 9 : 10-Diethyl- was found to react slightly less rapidly than 9 : 10-dimethyl-1 : 2-benzanthracene, as might be expected. The effect of methyl groups situated far from the point of addition was found to be small, or insignificant; *e.g.*, 6-methyl- (IX) and 5 : 6-dimethyl-1 : 2-benzanthracene reacted with osmium tetroxide only slightly more rapidly than benzanthracene; 5 : 6 : 9 : 10-tetramethyl- reacted only slightly more rapidly than 9 : 10-dimethyl-1 : 2-benzanthracene; and methylcholanthrene (X), which may conveniently be considered as a benzanthracene derivative substituted in positions 10, 5, and 6, reacted only slightly faster than cholanthrene.

The rate of addition of osmium tetroxide to acenaphthanthracene (4′ : 3-ace-1 : 2-benzanthracene) (XIII) is of particular interest, for this compound has a substituent methylene group at the point of addition. It was not expected that the presence of this group would prevent, by steric hindrance, the addition of osmium tetroxide to that double bond, and some interesting evidence which supports this view has been obtained. The complex, on hydrolysis, gave a *diol* (XIV), which on acetylation, yielded a *monoacetyl* derivative. This can



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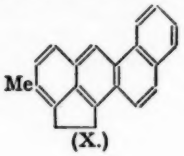

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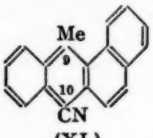

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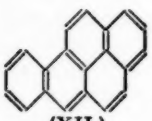
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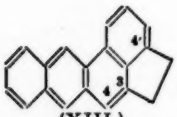

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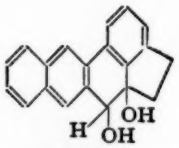

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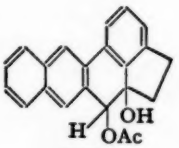

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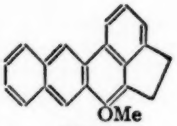


(XVI.)

only be explained if the methylene bridge offers steric hindrance towards one hydroxyl group, and the product was, almost certainly, 3-*hydroxy*-4-*acetoxy*-3 : 4-*dihydro*-4′ : 3-*ace*-1 : 2-*benzanthracene* (XV). Dehydration of the diol proceeded normally, to give the phenol, characterised as 4-*methoxy*-4′ : 3-*ace*-1 : 2-*benzanthracene* (XVI). In this connection, it is also of interest that Cook and Schoental (private communication) have found that osmium tetroxide adds normally to the 9 : 10-bond of 9-bromophenanthrene, to give a complex which, on hydrolysis, yields phenanthraquinone.

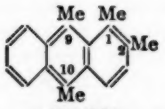
A cyano-group was found to deactivate the point of addition, for 10-cyano-1 : 2-benzanthracene reacted with osmium tetroxide very much more slowly than benzanthracene. Furthermore, 10-cyano-9-methyl-1 : 2-benzanthracene (XI), which presents the interesting combination of an electron-donating and an electron-attracting group, was found to react slightly less rapidly than benzanthracene. The deactivating influence of the cyano-group in the 10-position is therefore somewhat stronger than the activating influence of the methyl group in the 9-position.

6-Methyl-3 : 4-benzphenanthrene and 1 : 2 : 5 : 6-dibenzphenanthrene reacted with osmium tetroxide only slowly. It is possible that these compounds are less polarisable than benzanthracene derivatives, and in this connection it is noteworthy that Badger and Reed (*loc. cit.*) found phenanthrene very much less reactive than benzanthracene. 3 : 4-Benzpyrene (XII) and 1 : 2-dimethylchrysene were found to react moderately rapidly with osmium tetroxide, but 1 : 2 : 5 : 6-dibenzanthracene reacted only slightly more rapidly than 1 : 2-benzanthracene.

It is interesting to compare these results with the work of Eckhardt (*Ber.*, 1940, **73**, 13), who followed the rate of oxidation of some carcinogenic and related compounds with perbenzoic acid. The oxidation products have not been determined, and although the shape of some of the curves indicates that, in some cases, the reaction may be rather more complex than that with osmium tetroxide, it seems probable that the point of attack is the same. As is well known, perbenzoic acid reacts with ethylenic double bonds to form epoxides (Prileschajew, *Ber.*, 1909, **42**, 4811). It should be emphasised, however, that the mechanism of the perbenzoic acid reaction is almost certainly fundamentally different from that of osmium tetroxide addition. Eckhardt observed (i) an increase in the rate of oxidation following the introduction of a methyl group, and (ii) a decrease in the rate of oxidation following the introduction of the deactivating groups, CHO and NO_2.

Discussion.—It has long been recognised that nearly all the carcinogens of the polycyclic aromatic type are derivatives of phenanthrene. Indeed, certain alkyl derivatives of all the benzphenanthrenes (*viz.*, chrysene, 3 : 4-benzphenanthrene, and 1 : 2-benzanthracene), except triphenylene, are carcinogenic, although the position of the alkyl group is also of great importance. It must be admitted that relatively few homologues of triphenylene have been examined, but it does seem to be an exception, and this is of great interest, for in this hydrocarbon the chief feature of the phenanthrene ring system, namely, the 9 : 10-double bond, is absent. Furthermore, Hewett (*J.*, 1940, 293) has pointed out that the potent carcinogens are derivatives of phenanthrene substituted by fused benzene rings, or methyl groups, in three or four of the positions 1, 2, 3, and 4. Further substitution of 2 : 3-benzphenanthrene (*i.e.*, 1 : 2-benzanthracene) in either or both of the remaining 1- and 4-positions gives the highly carcinogenic hydrocarbons 9 : 10-dimethyl-1 : 2-benzanthracene, methylcholanthrene, 3 : 4-benzpyrene, etc. Further substitution of chrysene (1 : 2-benzphenanthrene) or of 3 : 4-benzphenanthrene gives the potent carcinogens 1 : 2-dimethylchrysene and 2-methyl-3 : 4-benzphenanthrene. On the other hand, all derivatives of phenanthrene are not carcinogenic. Of the 15 possible pentacyclic hydrocarbons in which each ring is 6-membered, 13 may be considered as derived from phenanthrene, but only 5 have given tumours; of the 8 non-carcinogenic derivatives, only one lacks a free 9 : 10-double bond (Barry *et al.*, *Proc. Roy. Soc.*, 1935, **117**, *B*, 318).

In order to determine whether the phenanthrene ring system is essential for carcinogenic activity in compounds of the polycyclic aromatic type, work was initiated, in 1938, on the synthesis of 1 : 2 : 9 : 10-tetramethylanthracene (XVII) and of 1 : 2 : 3 : 4-tetramethyl-



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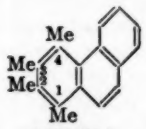

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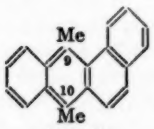
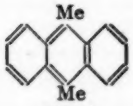


(XIX.)



(XX.)

phenanthrene (XVIII). Both hydrocarbons are structurally closely related to the potent carcinogen 9 : 10-dimethyl-1 : 2-benzanthracene (XIX). Tetramethylanthracene proved unexpectedly difficult to synthesise (Badger, Cook, and Goulden, *J.*, 1940, 16; Badger, Goulden, and Warren, *J.*, 1941, 18; Fieser and Webber, *J. Amer. Chem. Soc.*, 1940, **62**, 1360), and when it was eventually prepared (Sandin, Kitchen, and Fieser, *J. Amer. Chem. Soc.*, 1943, **65**, 2018) it was found to be unstable. 9 : 10-Dimethylanthracene (XX) was therefore examined (Badger, Goulden, and Warren, *loc. cit.*). Tetramethylphenanthrene was prepared by Hewett and Martin (*J.*, 1940, 1396). It was eventually shown that the phenanthrene ring system is not an essential requirement of a polycyclic aromatic hydrocarbon for carcinogenic activity, for both 1 : 2 : 3 : 4-tetramethylphenanthrene and 9 : 10-dimethylanthracene were found to be definitely if slightly carcinogenic (Badger *et al.*, *Proc. Roy. Soc.*, 1942, **131**, *B*, 170; Kennaway, Kennaway, and Warren, *Cancer Res.*, 1942, **2**, 157).

Further work, however, has again confirmed the importance of the phenanthrene ring system, and of the 9 : 10-bond in particular. Some interesting results have been obtained, for example, with compounds in which the 9 : 10-bond has been replaced by a sulphur atom (British Empire Cancer Campaign, Annual Report, 1946, 109). Sir Robert Robinson (*Brit. Med. J.*, 1946, i, 945) suggested that, although there are exceptions, an activated phenanthrene-type bridge appears to be implicated in most carcinogens.

In another approach to the problem, Pullman (*Ann. Chim.*, 1947, **2**, 5; Pullman and Pullman, *Experientia*, 1946, **2**, 364; *Rev. Sci.*, 1946, **84**, 145) suggested that carcinogenic activity is associated with an optimum density of π electrons on the phenanthrene-type bridge (hereinafter referred to, in accordance with Pullman, as the " K position "). Alkyl groups, especially methyl groups, act as slight donors of electrons to the ring, so that the substitution of methyl groups in suitable positions may increase the electron density at position K to more than the critical value for the development of carcinogenic activity. Quantum-mechanical calculations of the electron densities of several derivatives of 1 : 2-benzanthracene, 3 : 4-benzphenanthrene, 1 : 2-benzacridine, and 3 : 4-benzacridine were presented in support of the theory. Since osmium tetroxide attacks the K position, apparently without exception (Cook and Schoental, *loc. cit.*), this reaction offered an experimental method of testing the validity of the Pullman calculations.

On the whole, the present work appears to support, at least qualitatively, these calculations. On the other hand, it seems to the author that in assessing the validity of the correlation between

the electronic charge on the K position and carcinogenic activity, too little account has been taken of the numerous exceptions. On the basis of the Pullman theory, methylbenzanthracenes with methyl groups in the angular ring, should be carcinogenic. No calculations for these compounds were given. As a first approximation, however, one might expect that 4′-methyl-1 : 2-benzanthracene should have the same carcinogenic activity as 10-methyl-1 : 2-benzanthracene. In point of fact all the methylbenzanthracenes substituted in positions 1′, 2′, 3′, or 4′ are either completely inactive or have only trace activity. Inactive compounds of this type include: 1′-, 2′-, 3′-, and 4′-methyl-, 1′ : 10-, 2′ : 6-, 2′ : 7-, 3′ : 6-, and 3′ : 7-dimethyl-1 : 2-benzanthracene. It has been demonstrated by the present work that this criticism is valid, for 2′ : 7-dimethyl-1 : 2-benzanthracene was found to react rapidly with osmium tetroxide (see fig.). Furthermore, acenaphthanthracene, which is only slightly carcinogenic, reacted at the same rate as methylcholanthrene, one of the most potent of all the carcinogens.

Again a few carcinogens have been prepared which consist of a polycyclic structure substituted with a deactivating group. The cyano-group deactivates the ring, and this has been confirmed in the present instance by the demonstration that both 10-cyano-1 : 2-benzanthracene and 10-cyano-9-methyl-1 : 2-benzanthracene react with osmium tetroxide more slowly than does 1 : 2-benzanthracene. Nevertheless, the former compound is slightly carcinogenic and the latter is a particularly potent carcinogen.

The theory also takes no account of the fact, confirmed many times, that methyl derivatives of 3 : 4-benzphenanthrene, and of chrysene, are often potent when applied to the skin of mice, but show only feeble activity—or none at all—when administered by subcutaneous injection. The carcinogenic " grading " of such compounds is therefore a matter for some discussion. In any case, the grading used by Pullman (*loc. cit.*) for many of these derivatives appears to be unjustifiably high. 6-Methyl-3 : 4-benzphenanthrene is given ++, although it gave only one papilloma when applied to the skin of 20 mice in an experiment lasting nearly 2 years. Similar criticism applies to the 7-methyl- and 8-methyl-3 : 4-benzphenanthrenes, which have been found to be only very slightly active when applied to the skin, and completely inactive when administered by injection. (For these and other carcinogenic activities, the series of papers by Cook, Kennaway, and associates should be consulted: *Proc. Roy. Soc.*, **1932**, **111**, *B*, 455, 485; **1935**, **117**, *B*, 318; **1937**, **123**, *B*, 343; **1940**, **129**, *B*, 439; **1942**, **131**, *B*, 170. For further references see Hartwell, " Survey of compounds which have been tested for carcinogenic activity," 1941.) When re-graded in the light of these criticisms, these compounds become serious exceptions to the theory.

Experimental.

Materials.—(a) *Chloroform.* Chloroform B.P. was purified by shaking with concentrated sulphuric acid (at least twice), with water, dilute sodium hydroxide, and with several changes of water. After drying over calcium chloride, it was twice distilled, large head and tail fractions being discarded. These operations were carried out during one day, the purified chloroform being used for the preparation of standard solutions, and the reaction mixtures, on the following morning.

(b) *Osmium tetroxide.* This was used as obtained from the manufacturers, in 1 g. ampoules. Standard solutions were prepared by dissolving the contents of one ampoule (accurately weighed) in purified chloroform, at 20°, and making up to 50·0 ml. Such standard solutions, which were protected as much as possible from the light, were used within 48 hours.

(c) *Pyridine.* This was purified by prolonged boiling with potassium permanganate, followed by distillation over potassium hydroxide.

(d) *Hydrocarbons.* Pure synthetic materials were used.

(e) *Hydrocarbon–osmium tetroxide–pyridine complexes.* The complexes were prepared, in benzene, as described by Cook and Schoental (*loc. cit.*), and recrystallised by dissolving in chloroform containing a little pyridine, filtering, and adding light petroleum or benzene. The crystalline complexes separated on prolonged standing. (This method of recrystallisation was first used by Dr. R. Schoental.) A few complexes were also successfully recrystallised from boiling benzene.

Stability of the Benzanthracene Osmate–Pyridine Complex.—This was investigated by preparing standard solutions of the complex as follows: (i) in pure chloroform; (ii) in chloroform which had been purified and then exposed to air and light for a week (odour of carbonyl chloride very distinct); (iii) in chloroform B.P. from a recently opened bottle; (iv) as (i) but containing 4% of pyridine; (v) as (ii) but containing 4% of pyridine; (vi) as (iii) but containing 4% of pyridine. Samples (1 ml.) were removed as soon as the solution was made up, and diluted with a mixture of pyridine and chloroform (1 : 9) to 25·0 ml. Colour intensities were then estimated with the Spekker absorptiometer. Further samples were removed at convenient intervals. A significant change in " Spekker " reading indicated the instability of the solution. Solutions (i), (iv), (v), and (vi) were unchanged up to 24 hours. Solution (ii) was slightly turbid, gave a higher reading than the remainder, and darkened on standing. Solution (iii) gave increasing " Spekker " readings during 4 hours. When hydrogen chloride was passed into solution (i) it rapidly darkened.

Action of Osmium Tetroxide on Pyridine.—A solution of osmium tetroxide (0·5 g.) in pyridine (50 c.c.) was kept at room temperature, the yellow solution gradually becoming brown. After a week, crystals began to separate. After a month, the deposit (0·1 g.) was collected. The *complex* was insoluble in

chloroform, but was recrystallised from pyridine, forming light brown needles, or elongated prisms, which gradually decomposed, without melting (Found : Os, 45·75, 46·5. $OsO_4,2C_5H_5N$ requires Os, 46·15%). The same complex was obtained when solutions of osmium tetroxide and pyridine in chloroform were allowed to interact for a week or more.

Reaction.—The calculated quantity of the hydrocarbon was weighed, and washed into a standard flask with pure chloroform, at 20°. Pyridine, to give 4% in the reaction mixture, was then added. The flask was clamped in the thermostat, and the desired quantity of standard osmium tetroxide solution, at 20°, added. The mixture was quickly made up to the mark with chloroform, shaken, and the time taken. At suitable intervals 1-ml. samples were removed, and diluted to 25·0 ml. with a solution prepared from pyridine (50 ml.) and chloroform (450 ml.). The colour intensity of this solution was then estimated on the Spekker absorptiometer, green filters being used (Adam Hilger Ltd., " Spectrum Green, H, 604 "). The concentration of the complex was obtained from a calibration curve prepared from known concentrations of the complex. The effect of unreacted osmium tetroxide was estimated from a similar calibration curve of osmium tetroxide–pyridine at various concentrations. No correction was applied, however, for the reaction of osmium tetroxide with pyridine to give the brown complex.

For the comparison of the rates of addition to the carcinogenic compounds, standard conditions were used : hydrocarbon, 0·020M; osmium tetroxide, 0·0154M. 2′ : 7-Dimethyl-1 : 2-benzanthracene and 1 : 2 : 5 : 6-dibenzanthracene are sparingly soluble, and a completely homogeneous solution was not obtained at this concentration for the first 1—2 hours. The error due to this circumstance is not, however, thought to be large.

Identification of the Benzanthracene Reaction Product.—The reaction mixture remaining after the investigations with 1 : 2-benzanthracene was hydrolysed by shaking with an aqueous solution of potassium hydroxide (1%) and mannitol (10%). After 2 hours, the crude diol, m. p. 202—204° (decomp.) (lit., 202—204°) was filtered off. A portion was converted into the diacetoxy-compound by boiling with acetic anhydride and pyridine. After recrystallisation from light petroleum (b. p. 100—120°), 3 : 4-diacetoxy-3 : 4-dihydro-1 : 2-benzanthracene had m. p. 139—141°, not depressed by admixture with an authentic specimen, m. p. 142—143·5°.

Reaction with Acenaphthanthracene.—The complex was prepared as usual, in benzene, and hydrolysed with 1% aqueous potassium hydroxide containing 10% of mannitol, by shaking, in methylene chloride, for 2 hours. The *diol* (XIV) separated from benzene in colourless micro-needles, m. p. 215° (decomp.) (Found : C, 83·25; H, 5·6. $C_{20}H_{16}O_2$ requires C, 83·3; H, 5·6%). The *monoacetate* (XV) was prepared by 3 minutes' boiling with acetic anhydride containing a little pyridine. It separated from light petroleum (b. p. 100—120°) as fern-like clusters of colourless plates, m. p. 169—171° (Found : C, 80·0; H, 5·2. $C_{22}H_{18}O_3$ requires C, 80·0; H, 5·5%). The diol was dehydrated by brief boiling in acetic acid containing a few drops of hydrochloric acid. The crude phenol was immediately methylated with methyl sulphate and sodium hydroxide, at 100°. *4-Methoxy-4′ : 3-ace-1 : 2-benzanthracene* (XVI) separated from light petroleum (b. p. 100—120°) in very pale yellow needles or plates, m. p. 169—170° (Found : C, 88·6; H, 5·7. $C_{21}H_{16}O$ requires C, 88·7; H, 5·7%).

My thanks are due to Professor J. W. Cook, F.R.S., for his interest in this work, and for gifts of most of the hydrocarbons used. I am also grateful to Dr. R. I. Reed for many helpful discussions, to Mr. L. Hunter for the osmium analysis, and to Miss R. H. Kennaway for the other analyses. This work has been carried out during the tenure of an I.C.I. Research Fellowship.

UNIVERSITY OF GLASGOW. [*Received, May 25th,* 1948.]

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105. *A Theoretical Discussion of* o : p *Ratios and Orientation in Benzene Substitution.*

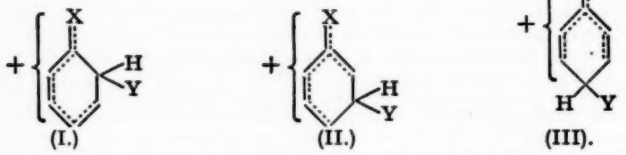
By M. J. S. DEWAR.

Wheland's method (*J. Amer. Chem. Soc.*, 1942, **64**, 900) has been used to investigate the relation between directive power and electron affinity of substituents in cationoid benzene substitution, and in particular the relation to *o* : *p* ratios in substitution. The general problem of orientation is then considered and the various factors discussed. The electrostatic treatment of reaction rates is criticised.

IT has long been known that substituents in benzene can be divided into two main classes, meta-directing and ortho–para-directing in cationoid substitution. An electronic interpretation of this distinction was given some time ago by Robinson [cf. " Outline of an Electro-chemical (Electronic) Theory of the Course of Organic Reactions ", Institute of Chemistry, 1932; *J. Soc. Dyers Col.*, Jubilee Issue, 1934, 65] and by Ingold (cf. *Chem. Reviews*, 1934, **15**, 225), and a quantum-mechanical justification for the earlier theory has been devised by Wheland (*J. Amer. Chem. Soc.*, 1942, **64**, 900). Two points still remain unclear however; the large variation in *o* : *p* ratios in benzene substitution, and the precise factor which determines the relative orienting power of substituents of the same type.

Wheland's method (*loc. cit.*) has now been extended in the hope of finding qualitative solutions to those two problems; and the whole problem of orientation is then discussed in a general way.

Method.—Following Wheland, we assume that the transition state for *o*-, *m*-, and *p*-cationoid substitution of a benzene derivative PhX by Y^+ have the mesomeric structures (I), (II), and (III) respectively; that the group CHY is similar in all three transition states; and that CHY does not conjugate with the rest of the ring. The activation energies for *o*-, *m*-, and *p*-substitution will then run parallel to the differences in total π-electron energy between PhX, and (I), (II), and (III) respectively. These assumptions seem reasonable first approximations, although CHY will probably hyperconjugate markedly with the ring—*i.e.*, the transition states will only approximate to these extreme quinonoid forms.



(I.) (II.) (III).

In calculating the π-electron energies by the simple molecular-orbital method, several new parameters are involved besides the usual C–C exchange integral β. These are (1) the C–X exchange integral γ; (2) the electron affinity of X relative to carbon δ; (3) the change in electron affinity of the annular carbons due to the inductive effect of X. To make the calculations manageable, some simplifying assumptions must be introduced.

First, it is likely, from considerations of π-bond energies, that for the usual substituents $\gamma \simeq \beta$, and moreover calculation shows that moderate variations in γ do not qualitatively alter the relative stabilities of (I), (II), and (III). Therefore the calculations have been carried out only for $\beta = 1$ (electromeric substituent) and $\beta = 0$ (inductive substituent). Secondly, if the polarisability of a bond is independent of field strength—a reasonable first approximation—the change in electron-affinity due to induction should die away along a carbon chain by a constant factor for each bond. We may therefore assume that the electron affinity of C_1 in PhX (the carbon linked to X) is $\varepsilon\delta$, of the *o*-carbons $\varepsilon^2\delta$, etc. This assumption is justified by some work by Branch and Calvin (cf. " The Theory of Organic Chemistry ", New York, 1941) who find that this relation holds in a number of cases with $\varepsilon \simeq \frac{1}{3}$. Since calculation shows that the conclusions reached here are not qualitatively affected by changes in ε, it has been assumed throughout that $\varepsilon = \frac{1}{3}$; so that the change in electron affinity of C_1 is $\delta/3$, of C_2 or C_6 $\delta/9$ etc.

Wheland calculated the subsidiary electron-affinity changes by a variation method, minimising the total π-electron energy. This procedure is both complicated and incorrect; for the changes in electron affinity are largely due to induction of σ-electrons, and Wheland neglects the corresponding changes in σ-electron energy. The present treatment seems at least equally valid.

A further, and much more serious, criticism of Wheland's method applies also to the present work. The application of the molecular-orbital method to ions, using the parameters that hold for neutral molecules, is not strictly justifiable. (This point has been discussed in detail elsewhere by Coulson and Dewar, *Trans. Faraday Soc.*, in course of publication.) However there are good grounds for believing that any errors so introduced will apply alike to all the calculations reported here, so that the relative values of the *o*-, *m*-, and *p*-activation energies should be reliable.

Substituents can be divided into three electronic types; pure inductive substituents, and anionoid and cationoid electromeric substituents. Those of the first type will be represented by the present model with $\gamma = 0$. As a model of an anionoid electromeric ($-E$) * substituent we may take X to be an atom with an unshared electron pair; thus there will be eight π-electrons to be fitted into the four lowest-energy orbitals of PhX, and six to fit into the three lowest-energy orbitals of (I), (II), and (III). As a model of a cationoid electromeric ($+E$) substitutent, we take X to be an atom with a vacant orbital; so that PhX will contain six π-electrons, and each transition state four.

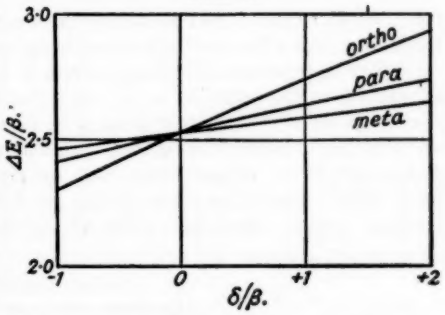
The calculations have been carried out for various values of δ ranging from -1 to 3, and the results are shown graphically in Figs. 1—3; the quantity ΔE being the difference in π-electron energy between PhX and the corresponding transition state, in units of β (in this approximation

* The sign convention of Robinson (*locc. cit.*) has been used throughout since it seems more logical than that of Ingold (*locc. cit.*). The latter would describe $-NMe_3^+$ as a negative, $-O^-$ as a positive substituent.

$\beta \simeq 18$ kcals./mol.). Calculation of dipole moments suggests that few, if any, substituents fall outside the range $-1 < \delta < 2$.

Conclusions.—The electronic theory of organic reactions assumes that differences in reaction rates are due only to activation energy differences, the steric factor (or the entropy of activation) being constant. With this assumption we can deduce from Figs. 1—3 the following rules for cationoid substitution of PhX, if in fact orienting power is determined mainly by the electron affinity of X.

FIG. 1.



(1) The overall rate of substitution should fall with increasing electron affinity of X for each class of substituent.

(2) For a $-I$ (anionoid inductive) substituent the order of rates should be $o > p > m$; for a $+I$ substituent, $m > p > o$. In both cases the spread of relative rates should increase with I-activity of X.

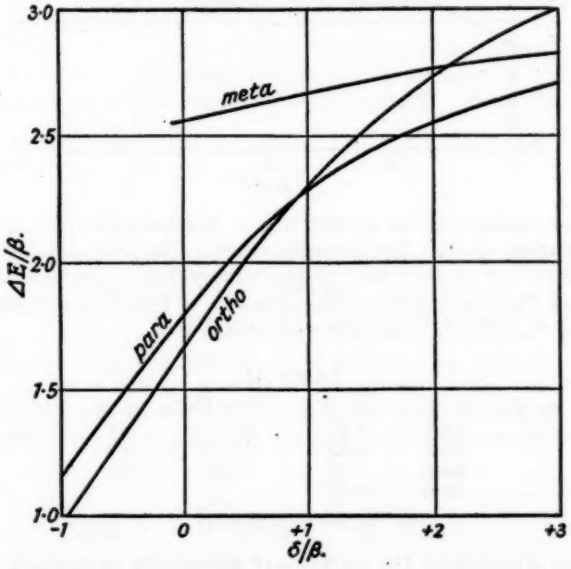
(3) For a $-E$ substituent, $(o, p) \gg m$; and with increasing δ, the ratio $o : p$ should fall. For $\delta = 0$, the ratio $o : p$ should be about unity.

(4) For a $+E$ substituent, $m \gg (o, p)$, and the directive power should increase with δ for normal values of δ; but the $o : p$ ratio should increase with δ in the same range. The $o : p$ ratio should always be considerably greater than unity.

Comparison with Experiment.—(1) It is well known that the rate of substitution in a series of similarly substituted benzenes falls with increasing electron affinity of the substituent. The

FIG. 2.

Anionoid electromeric (− E) substituent.



effect is shown clearly by the relative rates (benzene = 1) of nitration of the halogeno-benzenes under standard conditions, determined by Ingold and Shaw (*J.*, 1927, 2918), *viz.*, PhI >1, PhBr 0·36, PhCl 0·027, PhF 0·0107.

(2) The effect of increasing δ in an inductive substituent is shown well by the orientation of nitration in the ω-chlorotoluenes (Table I) [the data throughout this paper are taken from Holleman ("Die direkte Einfuhrung von Substituenten in den Benzolkern", 1910, and *Chem. Reviews*, 1925, **1**, 187) and Beilstein except where specifically stated]. Chlorine substituents, which increase the electron affinity of methyl, lower the $o : p$ ratio and increase the $m : (o, p)$ ratio (the ratios given are corrected for the statistical factor, and give the relative rates of substitution in single positions of each type). The $o : p$ ratios are smaller than the present discussion would

TABLE I

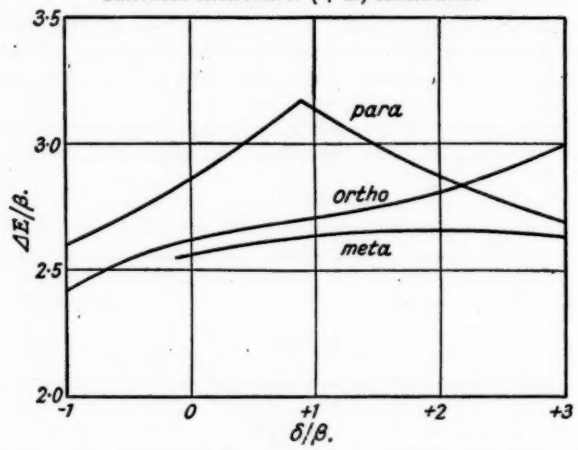
Compound.	*o*, %.	*m*, %.	*p*, %.	$\frac{1}{2}o : p$.	$\frac{1}{2}m : (\frac{1}{2}o + p)$.
$Ph{\cdot}CH_3$	58·8	4·4	36·8	0·80	0·03
$Ph{\cdot}CH_2Cl$	40·9	4·2	54·9	0·37	0·02
$Ph{\cdot}CHCl_2$	23·3	33·8	42·9	0·27	0·31
$Ph{\cdot}CCl_3$	6·8	64·5	28·7	0·12	1·09

lead one to expect; but this difference can probably be ascribed to slight steric hindrance, the frequency factor for *o*-substitution being smaller than for *p*- (see below).

Other compounds $Ph{\cdot}CH_2Z$, when Z has a high electron affinity (*e.g.*, $Ph{\cdot}CH_2{\cdot}\overset{+}{N}Me_3$), also substitute in the order $m > p > o$. Possibly $Ph{\cdot}SO_3H$ is another example; the $-SO_3H$ group seems to be a $+ I$ rather than a $+ E$ substituent, judging by its inefficiency in activating an adjacent methylene group. Substitution of $Ph{\cdot}SO_3H$ gives appreciable quantities of *p*-derivatives as by-products, but no detectable amount of *o*-. Diphenyliodonium nitrate, $Ph_2I^+NO_3^-$, also gives some (14%) *p*-, but no *o*-derivative on nitration (Sandin, McClure, and Irwin, *J. Amer. Chem. Soc.*, 1939, **61**, 3061).

FIG. 3.

Cationoid electromeric (+ E) substituent.



(3) The effect of increasing electron affinity in a $- E$ substituent is shown clearly by the data in Table II for nitration of the halogeno-benzenes. Electron affinity rises in the series $I < Br < Cl < F$, and the $o : p$ ratio falls in the same order. The effect is also shown by the $o : p$ ratios in the series Ph·Ph, Ph·NHAc, Ph·OMe, PhF (Table II); electron affinity rises along the series $Ph < NHAc < OMe < F$, and the $o : p$ ratio falls.

TABLE II.

X in PhX.	*o*, %.	*m*, %.	*p*, %.	$\frac{1}{2}o : p$.	X in PhX.	*o*, %.	*m*, %.	*p*, %.	$\frac{1}{2}o : p$.
I	41·1	—	58·7	0·35	Ph	53	—	47	0·56
Br	37·6	—	62·4	0·30	NHAc (*a*)	40·7	—	59·3	0·34
Cl	30·1	—	69·9	0·22	OMe	20	—	80	0·10
F	12·4	—	87·6	0·07					

(*a*) In 80% HNO_3.

Further evidence is provided by the nitration of acetanilide in strongly acid media. Under these conditions acetanilide forms a salt, $Ph{\cdot}NH{\cdot}CMe{:}\overset{+}{O}H$, and the group $NH{\cdot}CMe{:}\overset{+}{O}H$ must have a much higher electron affinity than —NHAc. Therefore increase in acidity of the solvent should lower the $o : p$ ratio, an effect shown by the data in Table III (nitration at —20°). It will be noticed that salt-formation does not alter the $o : p$ orienting effect of —NHAc. It is of course well known that salt-formation in aniline leads to *m*-direction, the group $-NH_3^+$

TABLE III.

Nitrating agent.	*o*, %.	*p*, %.	Nitrating agent.	*o*, %.	*p*, %.
80% HNO_3	40·7	59·3	HNO_3–90% H_2SO_4	4·5	95·5
90% HNO_3	24·5	75·5	HNO_3–100% H_2SO_4	—	100

having no electrons free for conjugation; this result confirms that the proton in $(Ph{\cdot}NHAcH)^+$ is attached to oxygen and not to nitrogen.

(4) Substitution of $+E$-substituted benzenes gives appreciable quantities of *o*-, but hardly any *p*-derivative, together with the dominant *m*-derivative. Some examples are given in Table IV; the $o:p$ ratio rises with increasing $+E$ activity, *i.e.*, in the series $CO_2Et < CO_2H < NO_2$, which is probably the order of increasing δ. (The data are for nitration at 0°.)

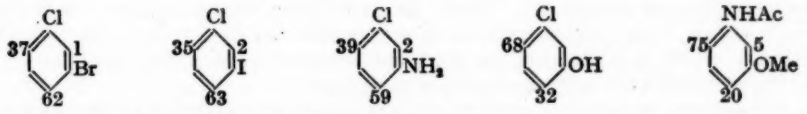
TABLE IV.

X in PhX.	*o*, %.	*m*, %.	*p*, %.	$\frac{1}{2}o:p$.	$\frac{1}{2}m:(\frac{1}{2}o+p)$.
CO_2Et	28·3	68·4	3·3	4·3	2·0
CO_2H	18·5	80·2	1·3	7·1	3·8
NO_2	6·4	93·2	0·25	12·8	13·5

No attempt has been made to calculate from the observed $o:m:p$ ratios the corresponding activation energy differences, and to compare these with values calculated from Figs. 1—3. Although the calculated values are of the right order of magnitude, lying in the range 0—5 kcals. for the values of δ to be expected from calculations of dipole moments, the whole method is too approximate to justify any such quantitative correlation.

Orientation in Polysubstituted Benzenes.—The present method could be extended to polysubstituted benzenes without difficulty, but the calculations would be tedious. Since, however, the effect of a substituent in benzene is only to perturb a mesomeric system already covering six nuclei, one might expect that to a first approximation the perturbations due to several different substituents in the same ring should be additive and so also their directive effect. This additivity was in fact established experimentally some time ago by Holleman (*locc. cit.*), and so the principles already laid down give a simple interpretation of substitution in the more complex cases. A few examples of orientation in two types of *m*-disubstituted benzenes will suffice; the data are for nitration, and the figures represent proportions of mononitro-derivative, while asterisks indicate the main points of attack when the proportions of isomers have not been determined.

(1) Both substituents $-E$. Substitution should occur almost exclusively in the 2 : 4 : 6-positions. Moreover, since most $-E$ substituents have $\delta > 0$, substitution should occur mainly para to the one with the higher electron affinity. From the following results :



it may be deduced that para-directive power rises in the series $I < Br < N < Cl < O$, which is probably also the series of increasing electron affinity.

(2) One substituent $+E$, one $-E$. Examination of Figs. 2 and 3 shows that for average values of δ, the $(o, p):m$ ratio for a $-E$ substituent should be greater than the $m:(o, p)$ ratio for a $+E$ one. Therefore in the present case substitution should occur *op* to the $-E$ substituent. Moreover since the $o:p$ ratio is usually small for $-E$ substituents, large for $+E$ ones, substitution should occur mainly para to the $-E$ substituent, the main by-product being the 1 : 2 : 3-derivative. The following examples illustrate these points :

Steric Hindrance.—Although the simple electronic treatment is thus generally satisfactory, its implied neglect of steric hindrance cannot be correct. Examination of models shows that in most *o*-disubstituted benzene derivatives, the substituents are closer than the sum of their van der Waals radii; the formation of such compounds must therefore be hindered, and the proportion of *o*-isomer should be less than that calculated from purely energetic considerations.

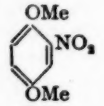
This effect appears to be small in most cases since the electronic theory is so successful and since, as Scheffer (*Proc. K. Akad. Wetensch. Amsterdam*, 1913, **15**, 1109, 1118) and Bradfield and Jones (*J.*, 1928, 1006) have shown, the frequency factors for *o*- and *p*-substitution are similar in many cases. However there is clear evidence that in substitution of PhX by Y^+, steric hindrance to *o*-substitution can be important if X or Y^+ is large.

Thus the ratio of frequency factors for *o*- to *p*-nitration of toluene is close to unity (0·75), but that for sulphonation is only 0·0053 (the ratios are calculated from the data of Holleman, *locc. cit.*). Nitration is little hindered, the active agent being the small NO_2^+ cation; but in sulphonation, where the active agent is probably the large ion $H_2SO_4^+$, *o*-substitution is greatly hindered.

The effect of enlarging X is shown very clearly in the series PhMe, PhEt, PhPr, PhBu^t, along which the *o* : *p* ratio falls. Quantitative data are lacking, but the effect is very marked, toluene giving more *o*-nitro-derivative than *p*-, while with PhBu^t only the *p*-nitro-derivative can be isolated. It seems impossible to explain these differences in electronic terms.

Special Effects.—(1) Chlorination or nitration of phenol gives *o*- and *p*-derivatives in comparable amounts, although phenol esters and ethers give much more *p*-isomer as the present arguments require. This difference might be due to a preliminary ionisation of the phenol, the agent substituted being Ph·O$^-$ and not Ph·OH; O$^-$ must have a relatively low electron affinity and should therefore give a relatively large *o* : *p* ratio. But bromination of phenol gives about 90% of *p*-bromophenol; and this difference cannot be due to steric hindrance since the ratio of *o*- to *p*-frequency factor is the same (~0·5) for both chlorination and bromination. It therefore seems quite likely that hydrogen-bonding in the transition state is responsible for the large *o* : *p* ratios in nitration and chlorination; hydrogen bonding is known to be important in *o*-nitrophenol and *o*-chlorophenol, but not in *o*-bromophenol.

(2) Another special effect is observed in 1 : 2 : 4-trisubstituted benzenes, where a $-E$ and a $+E$ substituent are ortho to one another. If the third substituent is $-E$, the main monosubstitution product is the 1 : 2 : 3 : 4-one. Thus (IV) gives mainly (V) on nitration, and (VI) gives (VII). This result is unexpected, since a simple application of the principles already



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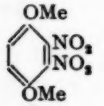

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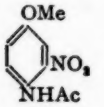

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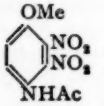
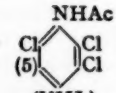


(VII.)



(VIII.)

discussed would suggest that a *m*-dinitro-compound should be formed in each case. The explanation is probably this; conjugation of the adjacent $-E$ and $+E$ groups tends to increase the bond-order of the annular bond between them, and so to cause an alternation of bond-order round the ring. The two groups (*e.g.*, NHAc, NO_2 in VI) are thus insulated from the rest of the ring by bonds of low order; substitution is therefore directed by the third group, and into the ortho position to which it is attached by the bond of higher order. This explanation could be checked by the methods used in the first part of this paper.

(3) Several authors have drawn attention to the effect on orientation of the steric inhibition of mesomerism between substituents and the ring (cf. Wheland, " The Theory of Resonance ", John Wiley, 1944). A good example is the nitration of 2 : 3 : 6-trichloroacetanilide (VIII) in the 5-position, a reaction quoted as anomalous by Holleman. Presumably the $-E$ effect of NHAc is sterically inhibited by the *o*-chlorine atoms; nitration occurs in the 5-positions, *op* to two chlorine atoms, the 4-position being only *o* to one.

Relation to Electrostatic Theories of Substitution.—A number of authors have tried to calculate activation energies on the assumption that they are due only to electrostatic interactions between the reagents (cf. Moelwyn-Hughes, " Reactions in Solution ", Oxford, 1947); and this concept has been applied to benzene substitution by Ri and Eyring (*J. Chem. Physics*, 1940, **8**, 433) and by Kenner (*Proc. Roy. Soc.*, 1946, *A*, **185**, 119). These calculations implicitly assume that reagents can approach to within bonding distance without appreciable distortion of their electron orbitals, and that they then react without activation. This is of course very far from being the case, reactions in general occurring by continuous adiabatic processes where the electron orbitals and charge distribution change continuously throughout. The electrostatic calculations are therefore quite worthless from an *a priori* point of view.

That they are moderately successful in practice would seem to be due to a general correlation between polarity and polarisability in most molecules. Consequently the energy of the transition state for attachment of a cation to some atom in a molecule runs inversely to the static negative charge on that atom in the unperturbed reactant. Therefore, although the electrostatic calculation gives a rough idea of the real activation energy in most cases, it does so only through a fortuitous correlation of two distinct effects.

Relation to the π-Complex Theory.—It has been suggested (Dewar, *J.*, 1946, 707) that the rate-determining step in substitution is the formation of a π-complex between the reagent and

reactant. This idea is not at variance with the main argument of the present paper, which discusses the orientation rather than the rate of substitution; and, as was emphasised earlier, the orientation will follow the same principles if transition states of the type considered in this paper are concerned, no matter whether or not their precursors are intermediate π-complexes.

One additional piece of evidence for the π-complex theory may be mentioned; Bennett, Brand, James, Saunders, and Williams (*J.*, 1947, 474) have found that the rate of nitration of dinitrotoluene (DNT) in sulphuric acid to trinitrotoluene (TNT) is given by

$$\frac{-\mathrm{d[DNT]}}{\mathrm{d}t} = k_1[\mathrm{DNT}][\mathrm{NO_2^+}]\{[\mathrm{HSO_4^-}] + k_2[\mathrm{H_2S_2O_7^-}] + k_3[\mathrm{H_2SO_4}]\}$$

They concluded that a termolecular reaction was involved. Since true termolecular reactions are virtually unknown in organic chemistry, it seems much more likely that an intermediate compound is formed reversibly from two of the reactants, this intermediate then reacting with the third reactant to give TNT. Such an intermediate would most reasonably be formulated as a π-complex, derived from DNT + NO_2^+. Since DNT must be a very poor electron donor, the π-complex should be unusually unstable; and its reversible formation, and failure to give TNT in absence of a base, would be easy to understand.

THE ISLET, MAIDENHEAD COURT, MAIDENHEAD, BERKSHIRE. [*Received, March 12th*, 1948.]

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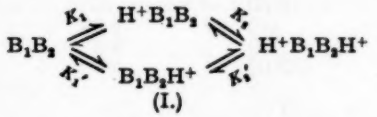
106. *Synthetic Antimalarials. Part XXXVI. Physicochemical Studies on Pyrimidine Derivatives.*

By J. C. GAGE.

The ultraviolet absorption spectra and electrolytic dissociation constants of certain pyrimidine derivatives containing a 2-diethylaminoethylamino-substituent have been measured and are discussed in relation to their structure and antimalarial activity. It is suggested that in this type of compound both the basic side chain and the heterocyclic nucleus must be ionised for the specific antimalarial activity to be exhibited.

IN Part XXXIV of this series (Gage, this vol., p. 221) an attempt has been made to correlate certain physical properties of the substituted diguanides with their structure and antimalarial activity. The discovery of high specific activity in members of this chemical type was preceded by the synthesis of active pyrimidine derivatives, and it was as a result of the formal similarities which can be demonstrated between the two types that the investigation into the antimalarial potentialities of the diguanides was undertaken (Curd and Rose, Part I, *J.*, 1946, 343; Part X, *ibid.*, p. 729). It is possible, therefore, that a more complete knowledge of the structure of the pyrimidines may increase our understanding of the antimalarial action of the diguanides.

Calculation of Dissociation Constants.—The four-component equilibria of an unsymmetrical diacid base B_1B_2, where B_1 is the more basic centre, may be represented by (I) (Irvin and Irvin, *J. Amer. Chem. Soc.*, 1947, **69**, 1091), where K_1, K_1', K_2, and K_2' are the equilibrium constants of the reaction of protons with the various proton acceptors, and K_1/K_2' and K_1'/K_2 are both equal to E, the electrostatic interaction between the two basic centres. In this communication K_1 and K_2 are regarded as the first and the second dissociation constant of the base B_1B_2; K_1 is therefore the equilibrium constant of the reaction of a proton with the more basic centre of B_1B_2, and K_2 is the constant of the reaction of the ion thus formed with a second proton. Irvin and Irvin (*loc. cit.*) have written the equilibrium in the reverse direction to that given in (I); their K_1 is concerned with the first-stage dissociation of $H^+B_1B_2H^+$. The definitions adopted here are preferred since they maintain the convention used by Christophers (*Ann. Trop. Med. Parasitol.*, 1937, **31**, 43; 1940, **34**, 1) in his study of the basicity of certain antimalarial drugs and which has been followed in Part XXXIV (Gage, *loc. cit.*). Irvin and Irvin, moreover, for calculating their potentiometric titration data, have followed Adam's definition (*J. Amer. Chem. Soc.*, 1916, **38**, 1503) of the two constants; for the spectrometric determination of the dissociation constant of $H^+B_1B_2H^+$ they have employed a constant K_3 with a different definition. When K_1 is very much less than K_1', the potentiometric titration constants of these authors approach the constants K_1 and K_2 which are used in this communication; and when $[H^+]$ is very much less than K_2', K_3 will also approach



(I.)

K_2. With a large group of compounds, which includes the pyrimidine derivatives studied in this investigation, the different definitions will lead to the same values for the dissociation constants; when compounds such as the alkylenediamines are investigated, which have K_1 and K_1' of the same order, the preferred definitions have the advantage of providing a simpler physical chemical interpretation, and they can be used for both the titrimetric and the spectrometric investigations.

Barton (*Nature*, **1947**, **160**, 752) has developed an equation for determining the constants K_1 and K_1' and the electrostatic term E from potentiometric titration data provided that one of them is known; for the equilibrium (I), the activity coefficients being neglected, this may be written in the form (1), where α, β, γ, and $[H^+]$ are measured values from the titration. If

$$\alpha/\gamma[H^+]^2 = \beta(1/K_1 + 1/K_1')/\gamma[H^+] + E/K_1K_1' \quad . \quad . \quad . \quad . \quad . \quad (1)$$

K_1/K_1' is of the order 0·2 or less, equation (1) does not yield accurate results, and it is not, therefore, suitable for the pyrimidine derivatives with which this communication is concerned. It may be used for the aliphatic diamines provided that K_1 is equal to K_1'; since the dissociation of an amino-group appears to be affected by the proximity of a second uncharged amino-group in the molecule (Table II), the value of K_1 or K_1' cannot be predicted from measurements on the alkylamines. Irvin and Irvin (*loc. cit.*) have used Reed and Berkson's analysis (*J. Physical Chem.*, **1929**, **33**, 760) as developed by Clark and Perkins (*J. Amer. Chem. Soc.*, **1932**, **54**, 1228) for redox titrations. The following treatment is simpler; it enables K_1 and K_2 as defined above to be calculated from potentiometric titration curves, and K_2 from spectrometric observations.

From a consideration of the principles of electroneutrality and the conservation of mass, equation (2) may readily be deduced, where C is the total molar concentration of base, and A is the number of moles neutralised. When K_2 is very much greater than $2[H^+]$, this reduces to (3), whence the dissociation exponent pK_1 is given by (4); similarly, when K_1 is very much less than $[H^+]$ the value of pK_2 is given by (5).

$$\frac{1 + K_1/K_1' + 2[H^+]/K_2}{1 + K_1/K_1' + K_1/[H^+] + [H^+]/K_2} = \frac{A + [OH^-] - [H^+]}{C} = y \quad . \quad . \quad . \quad (2)$$

$$K_1/[H^+] = (1 - y)/y(1 + K_1/K_1') \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

$$pK_1 = pH - \log_{10}[(1 - y)/y] - \log_{10}(1 + K_1/K_1') \quad . \quad . \quad . \quad . \quad (4)$$

$$pK_2 = pH - \log_{10}[(2 - y)/(y - 1)] + \log_{10}(1 + K_1/K_1') \quad . \quad . \quad . \quad (5)$$

The relative magnitudes of the dissociation exponents of the aliphatic tertiary amines and the aminopyrimidines given in Tables I and II, from which an approximation to K_1/K_1' can be

TABLE I.

With the exception of the new compound (IX), the antimalarial activities have been taken from previous communications in this series; the tests were performed against *P. gallinaceum* in chicks.

	Potentiometric titration.		Absorption spectra.		Antimalarial activity.	
Ref. in text.	pK_1.	pK_2.	pK_1.	pK_2.	Dose, mg./kg.	Activity
(II)	—	4·95	—	5·0	—	—
(III)	—	7·7	—	7·6	—	—
(V)	9·55	7·5	—	7·7	—	—
(VI)	9·8	6·85	—	7·1	—	—
(XIII)	9·7	7·9	—	—	80	++
					40	±
(VII)	—	—	—	6·6	—	—
(XVI)	9·1	6·2	—	—	160	+ to ±
					80	—
(VIII)	9·05	6·6	—	6·7	80	++
					40	+
(IX)	—	6·8	—	6·65	—	—
(X)	9·6	6·6	—	6·8	80	+
					40	—
(XI)	9·3	5·5	—	5·35	—	—
(XIV)	9·3	4·05	—	4·0	—	—
(XII)	9·8	8·33	—	(pK_2 = 1·9)	40	++
(XV; R = Cl)	—	—	10·0 *	—	—	—
(XV; R = NO_2)	—	—	9·4 *	—	—	—

* Refers to acid dissociation constant of hydroxyl group.

TABLE II.

Compound.		pK_1.	pK_2.	$\Delta pK = 10g_{10}\ 1/E$.
Triethylamine		10·8	—	—
Tetraethylethylenediamine:	0·01M	9·55	6·75	2·8
	4×10^{-4}M	9·3	6·65	2·65
Ethylenediamine:	0·01M	9·7	7·3	2·4

derived, indicate that for the dialkylaminoalkylaminopyrimidines the second logarithmic term in (4) and (5) can be neglected. From this approximate value of K_1K_1' it may be deduced that the concentration of the ion $B_1B_2H^+$ in the equilibrium (I) is negligible, but that it may not be possible to obtain a solution of the ion $H^+B_1B_2$ which is free from appreciable amounts of B_1B_2 or $H^+B_1B_2H^+$. It may not, therefore, be possible to determine the absorption spectrum of this ion with accuracy. The equation used in Part XXXIV (Gage, *loc. cit.*) may be modified so that the term signifying the extinction coefficient of the singly charged ion is eliminated. K_1 can be determined by measuring the optical density at two or more pH values selected so that the concentration of $H^+B_1B_2H^+$ is negligible; similarly, the measurements for K_2 are taken when the concentration of B_1B_2 is negligible. The constants are given by equations (6) and (7), where $\varepsilon_{B_1B_2}$ and $\varepsilon_{H^+B_1B_2H^+}$ are the molar extinction coefficients of B_1B_2 and $H^+B_1B_2H^+$, and ε' and ε'' are the extinction coefficients of solutions at hydrogen-ion concentrations $[H^+]'$ and $[H^+]''$. This method has been found more convenient than the graphical method of Vlés and Gex

$$K_1 = (\varepsilon' - \varepsilon'')/\{(\varepsilon_{B_1B_2} - \varepsilon')/[H^+]' - (\varepsilon_{B_1B_2} - \varepsilon'')/[H^+]''\} \quad . \quad . \quad . \quad . \quad (6)$$

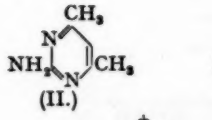
$$K_2 = \{[H^+]'(\varepsilon_{H^+B_1B_2H^+} - \varepsilon') - [H^+]''(\varepsilon_{H^+B_1B_2H^+} - \varepsilon'')\}/(\varepsilon - \varepsilon''). \quad . \quad . \quad . \quad (7)$$

(*Compt. rend.*, 1925, **180**, 1342). From the constants determined by equations (6) and (7) the optical density of $H^+B_1B_2$ at selected wave-lengths may be calculated.

The dissociation exponents obtained with the titrimetric and spectrometric methods are, in general, in good agreement. The experiments do not permit a statistical calculation of error, but it is probable that the great majority of the results by potentiometric titration are subject to an error of less than $\pm 0{\cdot}05$ unit. The precision of the spectrometric method depends on the magnitude of the difference between $\varepsilon_{B_1B_2}$ and $\varepsilon_{H^+B_1B_2H^+}$ at the chosen wave-length; as mentioned in Part XXXIV, the error can be minimised by replacing the extinction coefficients in (6) and (7) by the difference between the coefficients at two selected wave-lengths, and it is unlikely that any of the results are subject to an error of more than $\pm 0{\cdot}1$ unit.

Discussion of Results.—Formulæ (VIII), (XIII), and (XIV) are examples of pyrimidine derivatives showing specific antimalarial activity. All are characterised by a 2-diethylaminoethyl group attached to a substituted 2 : 4-diaminopyrimidine group through one of the amino-nitrogen atoms. These two basic centres give rise to two dissociation constants, and a comparison of the two dissociation exponents with those of the two isolated component groups (Tables I and II) indicates that the first (pK_1) may be attributed to the terminal nitrogen atom of the basic side chain, and the second (pK_2) associated with the heterocyclic group; to facilitate comparisons the dissociation exponents of the aminopyrimidines without the dialkylaminoalkyl group have been classified as pK_2 values

The basicity of 2-amino-4 : 6-dimethylpyrimidine (II) is appreciably increased by the replacement of a methyl by an amino-group (III), but there is no evidence from absorption spectra of the existence of a second basic centre in (III) in 0·1N-hydrochloric acid (Fig. 1). It may be reasoned, therefore, that the ion of (III) exists as a hybrid between the various resonance forms (IV).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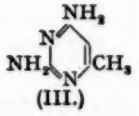
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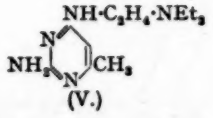
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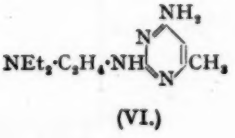
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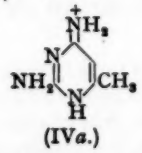
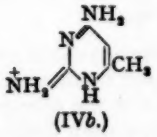
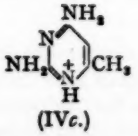
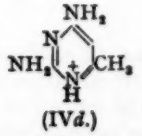

(IV*a*.)


(IV*b*.)

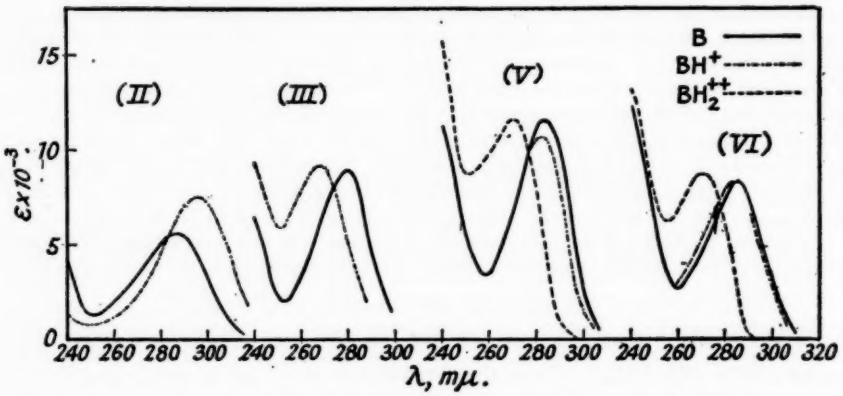

(IV*c*.)


(IV*d*.)

It is possible to locate the proton on the N_1 or the N_3 heterocyclic nitrogen, but it is reasonable to assume that the ion will be more stable when the charge concentration on the protonised

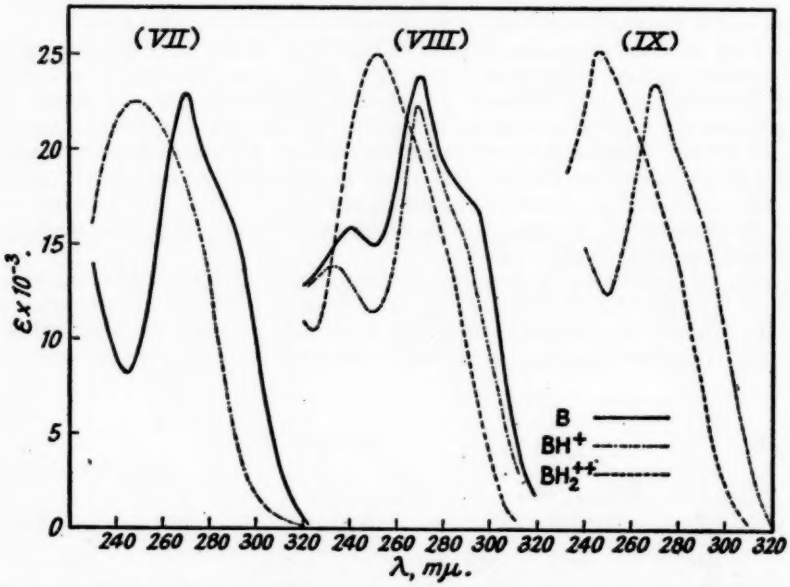
nitrogen is more remote from the charge distributed between the two amino-groups; that is, the ion with the proton on the N_1 nitrogen as in (IV) will have the lower energy. Moreover, (IV) permits the existence of a *p*-quinonoid form (IV*a*) in the ion; Albert and Goldacre (*Nature*, **1944**, **153**, 467) have discussed the greater stability of this form over the corresponding *o*-quinonoid structure. Derivatives of (III) with an amino-group replaced by a dialkylaminoalkylamino-group have been prepared (Hull, Lovell, Openshaw, Payman, and Todd, Part III, *J.*, **1946**,

FIG. 1.



357; Hull, Lovell, Openshaw, and Todd, Part XI, *J.*, 1947, 41); when a 2-diethylaminoethyl-amino-group replaces the 4-amino-group (V) there is no appreciable change in the dissociation of the heterocyclic system, but when this substituent replaces the 2-amino-group (VI) there is a significant decrease in basicity. It will be seen in Table II that the electro-negative inductive effect of the positive charge along the chain in the tetraethylethylenediamine ion is about

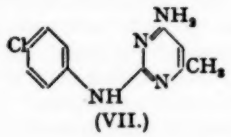
FIG. 2.

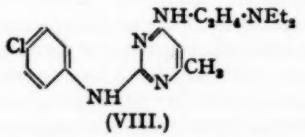


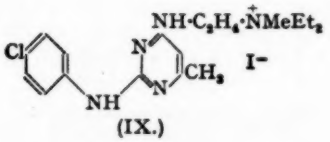
2·8 p*K* units. The absence of depression of the heterocyclic dissociation in (V) by the presence of this electro-negative substituent may be attributed to an attendant increase in the resonance energy of the ion which offsets the inductive effect of the charged basic side chain. This will obtain if the resonance form (IV*a*) is of a lower energy than (IV*b*), that is, if a greater proportion of the cationic charge is located on the 4- than on the 2-amino-group; the addition of the charged basic side chain to the former group will increase the energy of (IV*a*) and may make it

approach more closely to that of (IV*b*), thus increasing the resonance energy and the stability of the ion. In (VI) the electronegative effect of the charged side chain would be reinforced by a decrease in resonance energy resulting from a further separation of the energy levels.

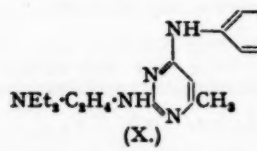
When the electronegative *p*-chloroanilino-group replaces the 2-amino-group (VII) there is also a decrease in basicity, but there is no further decrease when a charged basic side chain replaces the 4-amino-group (VIII); this is in accord with the above argument. Moreover, it is to be expected that the effect of changing the diethylaminoethyl group from the 2- to the 4-amino-group will diminish when a second electronegative group is attached to the unsubstituted amino-group; the more nearly the electron affinities of the two groups approach, the smaller will be the effect of interchanging them. No significant difference has been found between the pK_2 values of the two isomers (VIII) and (X). The absorption spectra of (VII) and (VIII) (Fig. 2) bear no obvious relation to those of (III) and (V), which suggests that the aryl and pyrimidine nuclei are not isolated by the bridging imino-group and migration of electrons is possible between them. In (VIII) the addition of a proton to the terminal nitrogen atom of the basic side chain is attended by a small change in absorption spectrum; this is sufficient only for an approximation of the pK_1 vlue. A more accurate pK_1 value can be obtained from potentiometric titration and, like those of mepacrine and pamaquin (Christophers, *Ann. Trop. Med. Parasitol.*, **1937**, **31**, 43; **1940**, **34**, 1), two active antimalarials which carry the same type of basic side chain, it is found to approach the pK_1 value of the tertiary amino-group in the corresponding aliphatic diamine. A comparison of the spectra of (VII), (VIII), and (IX) indicates that the absorption of the un-ionised heterocyclic system is slightly affected by the uncharged chain, but hardly at all by the charged or quaternised chain. There is no evidence from this of an interaction between the terminal nitrogen atom of the chain and the heterocyclic system.

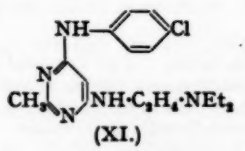

(VII.)

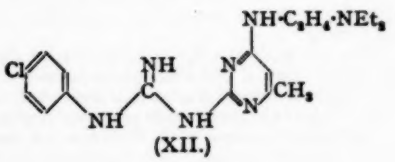

(VIII.)

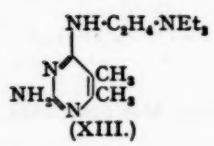

(IX.)

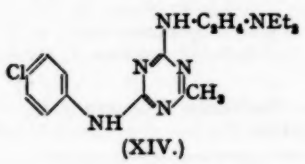
Formulæ (X) and (XI) represent isomers of (VIII) (Curd, Davis, Owen, Rose, and Tuey, Part VI, *J.*, **1946**, **370**; Basford, Curd, and Rose, Part VIII, *ibid.*, p. 713); the former, like (VIII), is an active antimalarial and has a similar pK_2 value, while the latter has a significantly lower pK_2 value and is without specific antimalarial activity. This observation suggests there may be some correlation between antimalarial activity and dissociation constants, a point which has previously been made by Christophers (*Trans. Faraday Soc.*, **1943**, **39**, 333). Additional support for this hypothesis is to be found in the antimalarials typified by the formulæ (XII) (Curd and Rose, Part IV, *J.*, **1946**, 362) and (XIII) (Hull, Lovell, Openshaw, Payman, and Todd, Part III, *ibid.*, p. 357), which show a higher antimalarial activity than (VIII) and also possess a higher pK_2 value. On the other hand, the triazine derivative (XIV) (Curd, Landquist, and Rose, Part XII, *J.*, **1947**, 154) shows a lower tendency to accept a proton on the heterocyclic system and is biologically inactive. It may tentatively be suggested that in this type of compound the heterocyclic system must exist to a significant extent in the ionised form at physiological pH values for the specific antimalarial activity to be apparent.

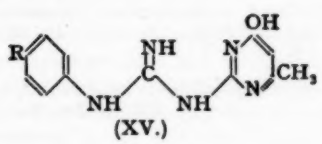

(X.)


(XI.)


(XII.)

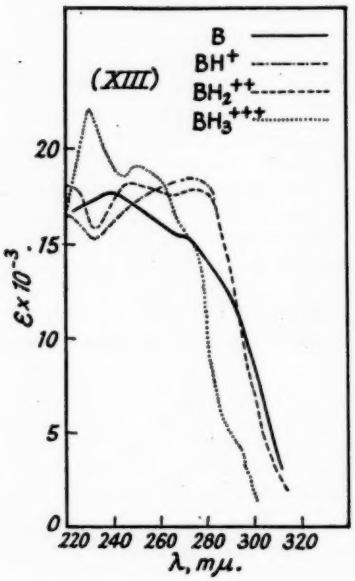

(XIII.)


(XIV.)


(XV.)

A high specific antimalarial activity has been obtained with 2-*p*-chlorophenylguanidino-4-2′-diethylamino-6-methylpyrimidine (XII). This compound has three dissociation constants; the pK_1 and pK_2 values are similar to those of (VIII), while the pK_3 value may be attributed to the guanidino-group linking the two rings. Two hydroxypyrimidine intermediates of (XIII) have been described by Curd and Rose (*loc. cit.*) (XV; R = Cl or NO_2); absorption spectra measurements show there to be a change in ionisation of these over the pH range 9—11. It is reasonable to ascribe this to the acidic dissociation of the hydroxyl group, as the values for (XII) indicate that a basic centre of the required strength is very improbable in this compound; and the calculated pK values show a significant difference which is in harmony with the observed difference in carbonate solubility. The suggestion advanced by Curd, Landquist, and Rose (*loc. cit.*) to account for this observation, *viz.*, that the molecule might exist to an appreciable extent in a fully conjugated form, is not supported by absorption-spectra measurements, which give no indication of an increased $\lambda_{max.}$ in (XII) over (VIII) (Fig. 3).

FIG. 3.



It has been suggested by Curd, Davey, and Rose (*Ann. Trop. Med. Parasitol.*, 1945, **39**, 157) that the specific antimalarial activity of pyrimidine derivatives such as (VIII) and (XII) is due to the antagonism of these compounds towards riboflavine, which they attribute to the formal resemblance between the drugs and the growth factor. Hull, Lovell, Openshaw, Payman, and Todd (*loc. cit.*) have suggested an analogous explanation for the activity of pyrimidine derivatives such as (XIII), with the drug-antagonising enzyme systems containing adenosine. This investigation is not designed to prove or disprove either of these hypotheses, which may well both be correct, but it does throw emphasis on the possibility that the pharmacodynamic group in both of these types may be the same and that the function of the substituents may be to achieve a favourable electron distribution. The effect of alkyl substituents in the pyrimidine nucleus on antimalarial activity provides the greatest challenge to this hypothesis; it is possible that the inactivity of (XV), a homologue of (VIII) without the 6-methyl group, may be connected with its lower pK_2 value, but this argument cannot be applied to the difference in activity between (V) and (XIII), since the pK_2 value of (V) is within the range of those compounds showing antimalarial activity.

EXPERIMENTAL.

A 0·01M-solution of tetraethylethylenediamine was titrated with 0·02N-hydrochloric acid, and a 4×10^{-4}M-solution in excess of hydrochloric acid was titrated with 0·01N-sodium hydroxide. The pyrimidine derivatives were obtained as the hydrochlorides; the non-aryl members were titrated at 0·01M-concentration with 0·02N-sodium hydroxide, while the lower solubility of the aryl derivatives necessitated a 4×10^{-4}M-solution titrated with 0·01N-alkali. The temperature was controlled at 25° ± 0·5°.

The dissociation exponents of the tetraethylethylenediamine were calculated by equations (9) and (10), $K/_1K_1'$ being assumed equal to unity, and are given in Table II. The exponents of the basic-side-chain pyrimidines were calculated by these equations on the assumption that the logarithmic term is negligible; this is not entirely justifiable for compound (XII), and its exponents may be subject to a slight error.

The method of determining the absorption spectra was the same as in Part XXXIV, with the exception that a chloride–phosphate–borate buffer, $8{\cdot}33 \times 10^{-3}$M to each anion, and with suitable addition of hydrochloric acid or sodium hydroxide, was used to control the hydrogen-ion concentrations.

The following *methiodide* was synthesised for this investigation.

2-p-*Chloranilino-4-2′-diethylaminoethylamino-6-methylpyrimidine 2′-Methiodide* (IX).—2-*p*-Chloranilino-4-2′-diethylaminoethylamino-6-methylpyrimidine (VIII) (8·4 g.) was dissolved in benzene (10 c.c.), and methyl iodide (4 g.) added. After 24 hours an insoluble resin was separated and recrystallised twice from alcohol–acetone to give a colourless solid, m. p. 165—166° (Found: C, 45·5; H, 5·85; N, 14·9; Cl, 7·75; I′, 26·1. $C_{18}H_{27}N_5ClI$ requires C, 45·4; H, 5·7; N, 14·7; Cl, 7·5; I′, 26·7%).

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[*Received, May 22nd*, 1948.]

107. *Synthetic Antimalarials. Part XXXVII. Some* N^1-p-*Chlorophenyl*-N^2 : N^4 : N^5-*trialkyldiguanides and Other Related Miscellaneous Diguanide Types.*

By R. DE B. ASHWORTH, A. F. CROWTHER, (the late) F. H. S. CURD, J. A. HENDRY, (MISS) D. N. RICHARDSON, and F. L. ROSE.

The reaction between guanidines and thioureas in presence of a desulphurising agent to give diguanides, first investigated by Cramer (*Ber.*, 1901, **34**, 2594), has been further explored, and it has been demonstrated that N^1-aryl-N^5-alkyldiguanides can be made, although in small yield, by condensing an arylguanidine with an alkylthiourea or by interaction of an arylthiourea with an alkylguanidine. Variants of these methods which have also been investigated comprise the reaction of *N*-aryl-*S*-alkyl*iso*thioureas with alkylguanidines and of *NS*-dialkyl*iso*thioureas with arylguanidines.

A number of N^1-*p*-chlorophenyl-N^2 : N^4-dialkyl-N^5-*iso*propyldiguanides have been made by the action of alkylamines, in presence of mercuric oxide, on *N*-(*N*-*p*-chlorophenyl-*N'*-alkylguanyl)-*N'-iso*propylthioureas which were obtained by the interaction of *iso*propyl *iso*thiocyanate and *N*-*p*-chlorophenyl-*N'*-alkylguanidines. An alternative route to the same type of compound was provided by the corresponding reaction of a *N*-*p*-chlorophenyl-*N'*-(*NN'*-dialkylguanyl)thiourea with an alkylamine.

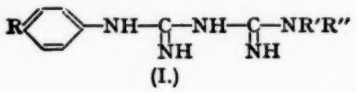
Analogous reactions have been employed for the preparation of a number of N^1 : N^2-diaryl-N^5-alkyldiguanides.

A number of N^2-alkylated derivatives of N^1-*p*-chlorophenyldiguanide have been made for biological comparison with the corresponding N^5-alkyl compounds (Part X, *J.*, 1946, 729), which possess high antimalarial activity, by the reaction of *N*-*p*-chlorophenyl-*N'*-guanylthiourea with alkylamines and mercuric oxide.

In previous papers of this series we have described the preparation of diguanides of type (II; R and R'' = alkyl, R' = H; and R and R' = alkyl, R'' = H) (Parts XXIX and XXX, *J.*, 1948, 1636, 1645) in which additional alkyl groups were attached to either N^3 or N^4 of the original highly active N^1-*p*-chlorophenyl-N^5-alkyldiguanide type (I; R = Cl, R' = H, R'' = alkyl) (see Part X, *loc. cit.*). Despite the fact that both these modifications produced a dystherapeutic effect on antimalarial activity (unpublished experiments by Dr. D. G. Davey) it was thought advisable to examine a few compounds in which alkyl groups were attached to both N^3 and N^4 (type II; R, R', R'' = alkyl).

The work of Cramer (*loc. cit.*), who condensed a number of *NN'*-diarylthioureas with guanidine in presence of mercuric oxide to give N^1 : N^2-diaryldiguanides and obtained N^1-phenyl-N^2-ethyldiguanide from *N*-phenyl-*N'*-ethylthiourea and guanidine by a similar reaction, suggested that an analogous synthetic method might be applied to the preparation of the desired compounds using a *N*-*p*-chlorophenyl-*N'*-alkylthiourea and a *NN'*-dialkylguanidine. It was decided, however, first to explore the applicability of the method to the preparation of the parent type (I), and when *p*-methoxyphenylguanidine (III; R = OMe, R' = H) was condensed with *iso*propylthiourea (IV; R = Pr^i, R' = H), in alcoholic solution in presence of mercuric oxide, a small but useful yield of N^1-*p*-methoxyphenyl-N^5-*iso*propyldiguanide (I; R = OMe, R' = H, R'' = Pr^i) was isolated as its *hydrochloride*. The identity of the product with that prepared by condensation of *p*-methoxyphenyl *iso*thiocyanate with *iso*propylguanidine (V; R = Pr^i, R' = R'' = H), followed by reaction of the resulting N-p-*methoxyphenyl*-N'-iso*propyl guanylthiourea* (VI; R = OMe, R' = R''' = H, R'' = Pr^i) with alcoholic ammonia in presence of mercuric oxide (cf. Part XXIX, *loc. cit.*), proved that the desired reaction had taken place. Similarly, a reverse type of synthesis, namely the condensation of *p*-chlorophenylthiourea (IV; R = *p*-C_6H_4Cl, R' = H) with *NN*-dimethylguanidine (V; R = R' = Me, R'' = H) proceeded to give N^1-*p*-chlorophenyl-N^5 : N^5-dimethyldiguanide (I; R = Cl, R' = R'' = Me) in about 6% yield, identical with the material described previously (Part X). However, only minute yields of N^1-*p*-chlorophenyl-N^5-*iso*propyldiguanide (I; R = Cl, R' = H, R'' = Pr^i) resulted from the condensation of *p*-chlorophenylguanidine (III; R = Cl, R' = H) with *iso*propylthiourea (IV; R = Pr^i, R' = H) and from the reaction of *p*-chlorophenylthiourea (IV; R = *p*-C_6H_4Cl, R' = H) with *iso*propylguanidine. Further, in an attempt to approach more closely the ultimate type of reaction projected, the condensation of *N*-*p*-chlorophenyl-*N'*-methylthiourea (IV; R = *p*-C_6H_4Cl, R' = Me) with *iso*propylguanidine led to no greater success, since only a very small yield of N^1-*p*-chlorophenyl-N^3-methyl-N^5-*iso*propyldiguanide (II; R = Pr^i, R' = H, R'' = Me) was isolated as its picrate. Condensation of *p*-chlorophenylguanidine with *p*-chlorophenylthiourea in presence of mercuric oxide was also disappoint-

ing in respect of the yield of N^1 : N^5-di-*p*-chlorophenyldiguanide (I; R = Cl, R′ = H, R″ = *p*-C_6H_4Cl) isolated.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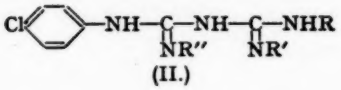
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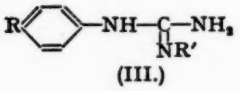
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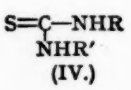
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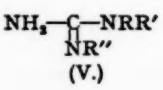
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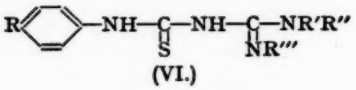
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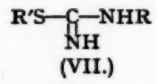
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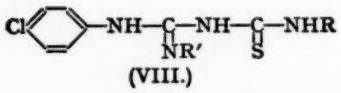
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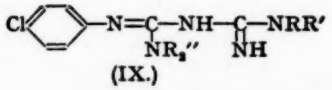
(IX.)

Attempts to utilise the *S*-alkyl*iso*thioureas in place of the thioureas themselves were likewise unpromising. Thus, interaction of *N*-*p*-chlorophenyl-*S*-methyl*iso*thiourea (VII; R = *p*-C_6H_4Cl, R′ = Me) with *iso*propylguanidine in boiling alcoholic solution gave only a small yield of (I; R = Cl, R′ = H, R″ = Pr^i) and the condensation of *NS*-dialkyl*iso*thioureas with arylguanidines gave no better results. Reactions of the latter type investigated, included the condensation of *S*-ethyl-*N*-*iso*propyl*iso*thiourea (VII; R = Pr^i, R′ = Et) hydriodide and of other *S*-alkyl derivatives of (IV; R = Pr^i, R′ = H) with *p*-chlorophenylguanidine to give N^1-*p*-chlorophenyl-N^5-*iso*propyldiguanide, the reaction of phenylguanidine (III; R = R′ = H) carbonate with NS-*di*iso*propyl*iso*thiourea* (VII; R = R′ = Pr^i) *hydrobromide* to give N^1-phenyl-N^5-*iso*propyldiguanide (I; R = R′ = H, R″ = Pr^i) and of *p*-chlorophenylguanidine with NS-*diethyl*iso*thiourea hydrobromide* (as VII; R = R′ = Et) to give (I; R = Cl, R′ = H, R″ = Et).

Since the above work indicated that a satisfactory method for the synthesis of the required compounds of type (II; R, R′, R″ = alkyl) would not be provided by an elaboration of the Cramer method, attention was directed to a modification of methods described in Parts XXIX and XXX (*locc. cit.*) for type (II; R and R″ = alkyl, R′ = H; and R and R′ = alkyl, R″ = H). *N*-*p*-Chlorophenyl-*N*′-methylguanidine (III; R = Cl, R′ = Me) was prepared by the action of methylamine on *N*-*p*-chlorophenyl-*S*-methyl*iso*thiourea (VII; R = *p*-C_6H_4Cl, R′ = Me), and reacted with *iso*propyl *iso*thiocyanate to give N-(N-p-*chlorophenyl*-N′-*methylguanyl*)-N′-iso*propylthiourea* (VIII; R = Pr^i, R′ = Me) *hydrochloride*. The constitution of this compound was settled by its conversion with alcoholic ammonia and mercuric oxide into the known N^1-*p*-chlorophenyl-N^2-methyl-N^5-*iso*propyldiguanide (II; R = Pr^i, R′ = H, R″ = Me), and, when methylamine was used in place of ammonia, N^1-p-*chlorophenyl*-N^3 : N^4-*dimethyl*-N^5-iso*propyldiguanide hydrochloride* (as II; R = Pr^i, R′ = R″ = Me) was obtained. The preparation of the same compound was then approached in another way, *p*-chlorophenyl *iso*thiocyanate being condensed with *N*-methyl-*N*′-*iso*propylguanidine (V; R = Pr^i, R′ = H, R″ = Me) to give N-p-*chlorophenyl*-N′-(N-*methyl*-N′-iso*propylguanyl*)*thiourea* (VI; R = Cl, R′ = Pr^i, R″ = H, R‴ = Me) which was converted into (II; R = Pr^i, R′ = R″ = Me) by the action of methylamine and mercuric oxide. Further analogous syntheses were then carried out. *iso*Propyl *iso*thiocyanate reacted with *N*-*p*-chlorophenyl-*N*′-ethylguanidine (III; R = Cl, R′ = Et) (prepared from *p*-chlorophenyl-*S*-methyl*iso*thiourea and ethylamine and characterised as its *picrate*) to give N-(N-p-*chlorophenyl*-N′-*ethylguanyl*)-N′-iso*propylthiourea* (VIII; R = Pr^i, R′ = Et); this by the action of ammonia, methylamine, and ethylamine in presence of a desulphurising agent gave respectively N^1-*p*-chlorophenyl-N^2-ethyl-N^5-*iso*propyldiguanide (II; R = Pr^i, R′ = H, R″ = Et), N^1-p-*chlorophenyl*-N^4-*methyl*-N^2-*ethyl*-N^5-iso*propyldiguanide* (II; R = Pr^i, R′ = Me, R″ = Et) *hydrochloride*, and N^1-p-*chlorophenyl*-N^3 : N^4-*diethyl*-N^5-iso*propyldiguanide* (II; R = Pr^i, R′ = R″ = Et) *hydrochloride*. The identification of the product from the ammonia reaction with that obtained from the interaction of N^1-*p*-chlorophenyl-N^2-ethyldicyandiamide with *iso*propylamine hydrochloride (see Part XXIX) served to prove not only its constitution but also the constitutions of the other two products.

The course of the above reactions between *p*-chlorophenyl *iso*thiocyanate and *N*-methyl-*N'*-*iso*propylguanidine on the one hand, and between *iso*propyl *iso*thiocyanate and *N*-*p*-chlorophenyl-*N'*-alkylguanidines on the other, was analogous to that of the corresponding condensations described in Part XXXIII (this vol., p. 98) in which a cyanamide was used in place of the *iso*thiocyanate. In all cases it was the unsubstituted NH-group of the guanidine which entered into the reaction, and this was in accord with the structure assigned to the product of interaction of phenyl *iso*thiocyanate and *NN'*-diphenylguanidine (Rathke, *Ber.*, 1887, **20**, 1072; Rathke and Oppenheim, *Ber.*, 1890, **23**, 1669). A similar method was then used to prepare a number of $N^1 : N^2$-diaryl-N^5-alkyldiguanides and their constitutions followed by analogy. *iso*Propyl *iso*thiocyanate was condensed with N-*phenyl*-N'-p-*chlorophenylguanidine* to give N-(N-*phenyl*-N'-p-*chlorophenylguanyl*)-N'-iso*propylthiourea* (VIII; R = Pr^i, R' = Ph) [cf. the reaction of methyl *iso*thiocyanate with *NN*-diphenylguanidine to give *N*-(*NN*-diphenylguanyl)-*N'*-methylthiourea, D.R.-P. 464,319] which was desulphurised with mercuric oxide in presence of ammonia to give N^1-phenyl-N^2-*p*-chlorophenyl-N^5-*iso*propyldiguanide (II; R = Pr^i, R' = H, R'' = Ph) isolated as its *acetate*. N^1-*p*-Chlorophenyl-N^2-*p*-tolyl-N^5-*iso*propyldiguanide (II; R = Pr^i, R' = H, R'' = *p*-C_6H_4Me) and $N^1 : N^2$-di-*p*-chlorophenyl-N^5-*iso*propyldiguanide (II; R = Pr^i, R' = H, R'' = *p*-C_6H_4Cl) were prepared similarly starting from N-p-*chlorophenyl*-N'-p-*tolylguanidine* and *NN'*-di-*p*-chlorophenylguanidine, while the reaction of N-(NN'-*di*-p-*chlorophenylguanyl*)-N'-iso*propylthiourea* (VIII; R = Pr^i, R' = *p*-C_6H_4Cl) with ethylamine in presence of mercuric oxide gave $N^1 : N^2$-*di*-p-*chlorophenyl*-N^4-*ethyl*-N^5-iso*propyldiguanide* (II; R = Pr^i, R' = Et, R'' = *p*-C_6H_4Cl).

The investigation of higher *N*-alkylated derivatives of the original N^1-*p*-chlorophenyl-N^5-alkyldiguanides included also the preparation of N^1-p-*chlorophenyl*-$N^2 : N^2$-*dimethyl*-N^5-iso*propyldiguanide* (IX; R = H, R' = Pr^i, R'' = Me) *hydrochloride* and of N^1-p-*chlorophenyl*-$N^2 : N^2 : N^5 : N^5$-*tetramethyldiguanide hydrochloride* (as IX; R = R' = R'' = Me) which resulted from the action of dimethylamine and mercuric oxide on *N*-*p*-chlorophenyl-*N'*-(*N*-*iso*propylguanyl)thiourea (VI; R = Cl, R' = Pr^i, R'' = R''' = H) and *N*-*p*-chlorophenyl-*N'*-(*NN*-dimethylguanyl)thiourea (VI; R = Cl, R' = R'' = Me, R''' = H) respectively.

Finally, for biological comparison with the corresponding N^1-*p*-chlorophenyl-N^5-alkyldiguanides, a number of N^1-*p*-chlorophenyl-N^2-alkyldiguanides were made by interaction of N-p'-*chlorophenyl*-N'-*guanylthiourea* (VI; R = Cl, R' = R'' = R''' = H) with alkylamines; the N^2-iso*propyl* compound (II; R = R' = H, R'' = Pr^i) from *iso*propylamine, the n-*propyl* compound (II; R = R' = H, R'' = Pr^n) from *n*-propylamine, and N^1-p-*chlorophenyl*-$N^2 : N^2$-*diethyldiguanide* (IX; R = R' = H, R'' = Et) from diethylamine.

Experimental.

Condensation of p-*Methoxyphenylguanidine with* iso*Propylthiourea.*—*p*-Methoxyphenylguanidine (6·6 g.), *iso*propylthiourea (4·72 g.), mercuric oxide (13 g.), and alcohol (50 c.c.) were stirred at 30—40° for 23 hours. 2N-Hydrochloric acid (100 c.c.) was added to the mixture followed by excess of sodium sulphide. The filtered mixture was then made alkaline with sodium hydroxide and extracted with benzene. Evaporation of the benzene left an oil which was dissolved in 2N-hydrochloric acid, and the solution filtered and neutralised with ammonia. Addition of salt precipitated the product which was collected, washed, and dried. It was dissolved in alcohol, and the solution filtered and precipitated with ethyl acetate to give N^1-p-*methoxyphenyl*-N^5-iso*propyldiguanide hydrochloride* which thereafter crystallised from alcohol–ethyl acetate as a colourless microcrystalline powder (yield, 4·4%), m. p. 231° (Found: C, 50·4; H, 7·1; N, 23·9; Cl, 12·5. $C_{12}H_{19}ON_5$,HCl requires C, 50·4; H, 7·0; N, 24·5; Cl, 12·4%).

N-p-*Methoxyphenyl*-N'-iso*propylguanylthiourea* (VI; R = OMe, R' = R''' = H, R'' = Pr^i).—*iso*Propylguanidine sulphate (23·8 g.) was added to acetone (100 c.c.) containing dissolved sodium (3·17 g.), and the mixture was stirred for 1 hour. *p*-Methoxyphenyl *iso*thiocyanate (17·5 g.) (Dyson and George, *J.*, 1924, **125**, 708) was then added, and the stirring continued for a further hour at 30°. The mixture was then drowned into water (1500 c.c.) and the resulting solid collected, washed with water, and dried. Crystallisation from benzene gave the *product* as colourless elongated prisms, m. p. 98° (Found: C, 54·5; H, 6·9; N, 21·0; S, 12·2. $C_{12}H_{18}ON_4S$ requires C, 54·1; H, 6·8; N, 21·05; S, 12·0%).

Conversion of N-p-*Methoxyphenyl*-N'-iso*propylguanylthiourea into* N^1-p-*Methoxyphenyl*-N^5-iso*propyldiguanide.*—The preceding compound (6 g.), mercuric oxide (12 g.), saturated alcoholic ammonia (30 c.c.), and alcohol (20 c.c.) were stirred at 30—35° for 16 hours, and the mixture was then acidified with hydrochloric acid and treated with sodium sulphide. After filtration and basification with sodium hydroxide, the liberated oil was isolated by extraction with benzene and evaporation of the benzene extract. It was then dissolved in 2N-hydrochloric acid, and the solution neutralised with ammonia and treated with salt. The resulting solid was collected, washed, dried, and crystallised from alcohol–ethyl acetate to give N^1-*p*-methoxyphenyl-N^5-*iso*propyldiguanide hydrochloride, m. p. and mixed m. p. 231°.

Condensation of p-*Chlorophenylthiourea with* NN-*Dimethylguanidine.*—Sodium (1·15 g., 0·05 g.-atom) was dissolved in alcohol (50 c.c.), *NN*-dimethylguanidine sulphate (6·7 g., 0·05 g.-mol.) added to the cold solution, and the mixture stirred at room temperature for 4 hours. *p*-Chlorophenylthiourea (3·2 g., 0·017 g.-mol.) and mercuric oxide (7·22 g., 0·034 g.-mol.) were then added, and stirring continued for

17 hours. The mixture was filtered and the residue washed with alcohol. The combined filtrate and washings were evaporated to dryness, and the residual gum extracted with 2N-hydrochloric acid (60 c.c.). The filtered extract was neutralised with ammonia, and the solid thereby precipitated filtered off, washed with water, and redissolved in dilute hydrochloric acid. The resulting solution was carbon-treated, filtered, and made alkaline with 10N-sodium hydroxide, whereupon small colourless needles of N^1-*p*-chlorophenyl-N^5 : N^5-dimethyldiguanide were precipitated (yield, 5·7%), m. p. 165—166° either alone or in admixture with an authentic specimen (Part X).

When sodium hydroxide was used in place of sodium in the above condensation and equimolecular quantities of *NN*-dimethylguanidine sulphate and *p*-chlorophenylthiourea employed, the main reaction product was not N^1-*p*-chlorophenyl-N^5 : N^5-dimethyldiguanide but *NN'*-di-*p*-chlorophenylguanidine (see below), m. p. and mixed m. p. 146—147° (Found: C, 55·7; H, 4·1; N, 15·2; Cl, 25·5. Calc. for $C_{13}H_{11}N_3Cl_2$: C, 55·7; H, 3·9; N, 15·0; Cl, 25·4%).

Condensation of p-*Chlorophenylguanidine with* iso*Propylthiourea.*—*p*-Chlorophenylguanidine (3·39 g.), *iso*propylthiourea (2·36 g.), and lead monoxide (8·9 g.) were boiled in alcohol (50 c.c.) for 18 hours with stirring. The mixture was then cooled and filtered, and the residue washed with alcohol. The combined filtrate and washings were evaporated to dryness, and the residue extracted with 2N-hydrochloric acid. The filtered extract was then added to excess of ice-cold 5N-sodium hydroxide, and the precipitated base isolated by extraction with benzene and evaporation of the dried (K_2CO_3) extract. The base was dissolved in ethyl acetate, and acetic acid added to render the solution faintly acid to litmus. On standing, N^1-*p*-chlorophenyl-N^5-*iso*propyldiguanide acetate separated (yield, 1·6%), m. p. 187°, undepressed in admixture with an authentic specimen (Part X).

Condensation of p-*Chlorophenylthiourea with* iso*Propylguanidine.*—Sodium (0·92 g.) was dissolved in dry acetone (35 c.c.) at 30°, *iso*propylguanidine sulphate (6 g.) added, and the mixture stirred for 2 hours at 20—30°. *p*-Chlorophenylthiourea (7·46 g.) and mercuric oxide (17 g.) were then added, and the mixture stirred at room temperature for 19 hours and filtered, the residue being washed with acetone. Evaporation of the combined filtrate and washing left a gum which was extracted with benzene. The benzene extract was shaken with 2N-hydrochloric acid, and the acid solution was separated and treated with ammonium chloride, copper sulphate solution, and sodium hydroxide to render it strongly alkaline. The copper complex of the diguanide was extracted with benzene, and the benzene solution in turn extracted with 2N-hydrochloric acid. Sodium sulphide was added to the acid extract which was filtered and then made strongly alkaline with sodium hydroxide and extracted with benzene. After evaporation of the dried benzene extract, the residue was dissolved in dry ethyl acetate (7 c.c.), and acetic acid added to give an acid reaction to litmus; a small amount of crystalline material then separated, and was collected and identified as N^1-*p*-chlorophenyl-N^5-*iso*propyldiguanide acetate (yield, 0·8%), m. p. and mixed m. p. 187°.

Condensation of N-p-*Chlorophenyl*-N'-*methylthiourea with* iso*Propylguanidine.*—*iso*Propylguanidine sulphate (5·7 g.) was added to a solution of sodium hydroxide (1·4 g.) in alcohol (40 c.c.), and the mixture stirred at room temperature for 1 hour. *N*-*p*-Chlorophenyl-*N'*-methylthiourea (7 g.) (Hunter and Jones, *J.*, 1930, 2203) and mercuric oxide (14 g.) were then added, and the mixture stirred at 30—40° for 18 hours. 2N-Hydrochloric acid and excess of sodium sulphide were added, the mixture filtered, and the filtrate made strongly alkaline with sodium hydroxide. The liberated oil was extracted with benzene, and the benzene solution dried (K_2CO_3) and evaporated. The residue was dissolved in acetic acid, treated with methanolic picric acid, and diluted with water. The precipitated oily picrate was separated by decantation and triturated with methanol, whereupon it solidified. Crystallisation from aqueous methanol afforded N^1-*p*-chlorophenyl-N^3-methyl-N^5-*iso*propyldiguanide picrate (cf. Part XXIX), m. p. and mixed m. p. 163—164° (Found: N, 22·8. Calc. for $C_{13}H_{18}N_5Cl,C_6H_3O_7N_3$: N, 22·6%).

Condensation of p-*Chlorophenylthiourea with* p-*Chlorophenylguanidine.*—*p*-Chlorophenylthiourea (3·73 g.), *p*-chlorophenylguanidine (3·39 g.), and lead monoxide (8·9 g.) were boiled in alcohol (50 c.c.) for 18 hours. The mixture was then filtered and the filtrate evaporated to dryness. The residue was dissolved in alcoholic hydrogen chloride and the solution evaporated to dryness. Crystallisation of the residue from alcohol–ethyl acetate gave N^1 : N^5-di-*p*-chlorophenyldiguanide hydrochloride (yield, 3·1%), m. p. 250°, either alone or in admixture with an authentic specimen (see Part XXIX, *loc. cit.*).

Condensation of N-p-*Chlorophenyl*-S-*methylisothiourea with* iso*Propylguanidine.*—Sodium hydroxide (0·8 g.) was dissolved in alcohol (20 c.c.), and *iso*propylguanidine sulphate (3 g.) added. After 1 hour's stirring at room temperature, *N*-*p*-chlorophenyl-*S*-methyl*iso*thiourea (4 g.) (Part XXV, Crowther, Curd, and Rose, *J.*, 1948, 586) was added, and the mixture refluxed for 30 hours with stirring. It was then poured into water (100 c.c.) and made acid to Congo-red with hydrochloric acid, and the solution was carbon-treated and filtered. The filtrate was made strongly alkaline with sodium hydroxide, and shaken with benzene and ammoniacal copper sulphate solution. The benzene layer was separated, washed with water, and extracted with 2N-hydrochloric acid. The acid extract was freed from copper salts by the addition of sodium sulphide and filtration. The filtrate was then made alkaline with sodium hydroxide and extracted with benzene, and the benzene extract dried and evaporated. The residue, dissolved in ethyl acetate and treated with acetic acid, afforded N^1-*p*-chlorophenyl-N^5-*iso*propyldiguanide acetate (yield, 3·1%), m. p. 187°, either alone or in admixture with an authentic sample.

S-*Ethyl*-N-iso*propyl*iso*thiourea* (VII; R = Pr^i, R' = Et).—*iso*Propylthiourea (2·36 g.) (May, *J. Org. Chem.*, 1947, **12**, 437), ethyl iodide (3·5 g.), and alcohol (10 c.c.) were refluxed for ½ hour, and the mixture evaporated to dryness to leave *S*-ethyl-*N*-*iso*propyl*iso*thiourea hydriodide as an oil which could not be crystallised.

*iso*Propylthiourea (11·8 g.), treated with ethyl bromide (12 g.) in alcohol (50 c.c.) under reflux for 18 hours, gave the corresponding *hydrobromide* which was isolated by evaporation to dryness and stirring the residual solid with ethyl acetate (yield, 21·7 g.); m. p. 126—128° (Found: C, 31·9; H, 6·5; N, 12·3. $C_6H_{14}N_2S$,HBr requires C, 31·7; H, 6·6; N, 12·3%).

Condensation of S-*Ethyl*-N-iso*propyl*iso*thiourea Hydriodide with* p-*Chlorophenylguanidine.*—The above oily *S*-ethyl-*N*-*iso*propyl*iso*thiourea hydriodide, (5·5 g.), *p*-chlorophenylguanidine (3·7 g.), and alcohol (20 c.c.) were refluxed for 18 hours. Ethylthiol was evolved. The solution was then evaporated to

dryness, and the residue treated with sodium hydroxide and extracted with ether. The ether extract was shaken with 5% acetic acid, the acid extract separated, and made alkaline with sodium hydroxide, and the product again extracted with ether. The ether extract was dried and evaporated, the residue dissolved in acetone, and the alkalinity destroyed by the addition of acetic acid. On scratching, a small crop of crystalline material was obtained which proved to be N^1-*p*-chlorophenyl-N^5-*iso*propyldiguanide acetate, m. p. and mixed m. p. 185° (Found: C, 49·4; H, 6·2; N, 22·3. Calc. for $C_{11}H_{16}N_5Cl,C_2H_4O_2$: C, 49·7; H, 6·4; N, 22·3%).

NS-*Diisopropylisothiourea* (VII; R = R′ = Pr^i).—Prepared in the same way as the *S*-ethyl compound described above, the *hydrobromide* had m. p. 134—136° (Found: C, 34·6; H, 6·8; N, 11·6. $C_7H_{16}N_2S$,HBr requires C, 34·9; H, 7·1; N, 11·6%).

Condensation of NS-*Diisopropylisothiourea Hydrobromide with* p-*Chlorophenylguanidine*.—*NS*-Di-*iso*propyl*iso*thiourea hydrobromide (2·5 g.), *p*-chlorophenylguanidine (1·7 g.), and alcohol (10 c.c.) were refluxed for 24 hours, and the product worked up as in the similar reaction described above, to give a very small yield of N^1-*p*-chlorophenyl-N^5-*iso*propyldiguanide acetate, m. p. and mixed m. p. 185°.

S-*Benzyl*-N-iso*propylisothiourea* (VII; R = Pr^i, R′ = CH_2Ph).—*iso*Propylthiourea (11·8 g.) and benzyl chloride (14 g.) were boiled in alcohol (50 c.c.) for 15 hours. The mixture was evaporated to small bulk, and ethyl acetate added to precipitate the *hydrochloride* (yield, 23·5 g.), which crystallised from water, m. p. 147—148° (Found: C, 54·0; H, 7·1; N, 11·6. $C_{11}H_{16}N_2S$,HCl requires C, 54·0; H, 6·95; N, 11·5%). A solution of the hydrochloride in water added to 2N-sodium hydroxide gave the *base* which, after drying, crystallised from light petroleum (b. p. 80—100°) as colourless glistening needles, m. p. 67—68° (Found: C, 63·2; H, 7·4; N, 13·1. $C_{11}H_{16}N_2S$ requires C, 63·5; H, 7·7; N, 13·5%).

Condensation of S-*Benzyl*-N-iso*propylisothiourea Hydrochloride with* p-*Chlorophenylguanidine*.—*p*-Chlorophenylguanidine (1·7 g.) and *S*-benzyl-*N*-*iso*propyl*iso*thiourea hydrochloride (2·5 g.) were heated in boiling alcohol for 24 hours. The mixture was evaporated to dryness, and the residue treated with water (10 c.c.) and hydrochloric acid (5 c.c.) and extracted with ether. The acid solution was made alkaline to brilliant-yellow with ammonia; a small amount of oil then separated. This gradually solidified, and was then collected, dried, and triturated with ethyl acetate. Crystallisation from water gave N^1-*p*-chlorophenyl-N^5-*iso*propyldiguanide hydrochloride (0·5 g.), m. p. and mixed m. p. 244—245°.

Condensation of Phenylguanidine Carbonate with NS-*Diisopropylisothiourea Hydrobromide*.—Phenylguanidine carbonate (1·7 g.), *NS*-di*iso*propyl*iso*thiourea hydrobromide (2·5 g.), and alcohol (10 c.c.) were boiled under reflux for 24 hours, and the solution then evaporated to dryness under reduced pressure. The residue was treated with 2N-sodium hydroxide and extracted with ether. The ether extract was washed with water and then extracted with 5% acetic acid. The acid extract was made alkaline with sodium hydroxide and extracted with ether, and the ether extract washed, dried (Na_2SO_4), and evaporated. The residual oil was dissolved in 2-ethoxyethanol, and 2-ethoxyethanolic hydrogen chloride added until alkalinity to brilliant-yellow had been destroyed. After addition of ethyl acetate, crystallisation of the product was induced by scratching. When separation was complete the product was collected, washed with ethyl acetate, and dried. Crystallisation from water gave material (yield, 0·2 g.), m. p. 235—236° undepressed in admixture with N^1-phenyl-N^5-*iso*propyldiguanide hydrochloride (Part XXVIII, *loc. cit.*).

NS-*Diethylisothiourea* (VII; R = R′ = Et).—Prepared from ethylthiourea and ethyl bromide as in the case of similar compounds, the *hydrobromide* had m. p. 77—79° (Found: C, 28·0; H, 5·9; N, 13·2. $C_5H_{12}N_2S$,HBr requires C, 28·2; H, 6·1; N, 13·15%).

Condensation of p-*Chlorophenylguanidine with* NS-*Diethylisothiourea Hydrobromide*.—*p*-Chlorophenylguanidine (1·7 g.), *NS*-diethyl*iso*thiourea hydrobromide (2·2 g.), and alcohol (10 c.c.) were refluxed for 24 hours. The mixture was then evaporated to dryness, and the residue treated with sodium hydroxide and extracted with ether. The ether extract was shaken with 5% acetic acid, and the acid extract made alkaline and re-extracted with ether. Evaporation of the washed and dried ether extract left a base which was converted into its acetate by treatment with acetic acid in acetone. The very small amount of material (<0·2 g.) obtained, was identified as N^1-*p*-chlorophenyl-N^5-ethyldiguanide acetate (Part X), m. p. and mixed m. p. 160—161°.

N-p-*Chlorophenyl*-N′-*methylguanidine* (III; R = Cl, R′ = Me).—*N*-*p*-Chlorophenyl-*S*-methyl*iso*thiourea (10 g.), methylamine (25 c.c. of 21% solution), and alcohol (20 c.c.) were heated in a closed vessel at 80—90° for 4 hours. The mixture was then evaporated to dryness and the residue crystallised from toluene and then from benzene. Material of constant m. p. could not be obtained, but it was shown to be substantially *N*-*p*-chlorophenyl-*N*′-methylguanidine since it afforded the *picrate* which crystallised from alcohol as yellow needles, m. p. 90°, then solidifying and remelting at 151—152° (Found: C, 40·8; H, 3·1; N, 20·8. $C_8H_{10}N_5Cl,C_6H_3O_7N_3$ requires C, 40·7; H, 3·2; N, 20·4%).

N-(N-p-*Chlorophenyl*-N′-*methylguanyl*)-N′-iso*propylthiourea* (VIII; R = Pr^i, R′ = Me).—A mixture of N-*p*-chlorophenyl-N′-methylguanidine (9·9 g.) and *iso*propyl *iso*thiocyanate (4·4 g.) was heated on the steam-bath for 4 hours. The mixture was then steam-distilled to remove unchanged *iso*thiocyanate, and the residue separated by decantation and dissolved in alcohol (20 c.c.). Addition of 10N-hydrochloric acid to this solution to render it faintly acid to Congo-red precipitated the *hydrochloride* as an oil which soon crystallised. Recrystallised from alcohol–ethyl acetate it formed colourless prisms, m. p. 171° (Found: C, 44·8; H, 5·8; N, 17·3; Cl, 22·2. $C_{13}H_{17}N_4ClS$,HCl requires C, 44·9; H, 5·6; N, 17·4; Cl, 22·1%).

Reaction of N-(N-p-*Chlorophenyl*-N′-*methylguanyl*)-N′-iso*propylthiourea with Ammonia*.—The above hydrochloride (2 g.), mercuric oxide (4 g.), and alcoholic ammonia (35 c.c. of 13%) were stirred at 30—40° for 20 hours. The mixture was acidified with dilute hydrochloric acid, treated with excess of sodium sulphide, and filtered. The filtrate was made alkaline with sodium hydroxide, and the precipitated base extracted with benzene. The base left on evaporation of the dried benzene extract was dissolved in alcoholic hydrogen chloride, ethyl acetate added, and the precipitated material crystallised from alcohol–ethyl acetate to give N^1-*p*-chlorophenyl-N^5-methyl-N^5-*iso*propyldiguanide hydrochloride, m. p. 166—168°, undepressed in admixture with an authentic sample (Part XXIX, *loc. cit.*).

N-*Methyl*-N′-iso*propylguanidine* (V; R = H, R′ = Pr^i, R″ = Me).—*iso*Propylthiourea (4·3 g.),

methyl iodide (2·5 c.c.), and alcohol (5 c.c.) were warmed gently. When the ensuing vigorous reaction had subsided the mixture was refluxed for 1 hour and then evaporated to dryness. The residual syrup of *S*-methyl-*N*-*iso*propylthiourea hydriodide could not be induced to crystallise (cf. the corresponding *S*-ethyl derivative above), and was therefore heated with 21% aqueous methylamine (6·2 g.) for 16 hours at 100° in a closed vessel. Evaporation of the mixture gave *N*-methyl-*N'*-*iso*propylguanidine hydriodide as a colourless syrup which could not be induced to crystallise. An aqueous solution of a small portion treated with methanolic picric acid gave the *picrate* which separated from water as yellow needles, m. p. 148° (Found: C, 38·8; H, 4·6; N, 24·4. $C_5H_{13}N_3,C_6H_3O_7N_3$ requires C, 38·4; H, 4·65; N, 24·4%).

N-p-*Chlorophenyl*-N'-(N-*methyl*-N'-iso*propylguanyl*)*thiourea* (VI; R = Cl, R' = Pr^i, R'' = H, R''' = Me).—Sodium (0·57 g.) was dissolved in dry acetone (30 c.c.), *N*-methyl-*N'*-*iso*propylguanidine hydriodide (9 g.) added, and the mixture stirred at 20—30° until homogeneous. *p*-Chlorophenyl *iso*thiocyanate (4·2 g.) was then added, and the mixture stirred at 30° for 1·5 hours. The clear mixture was poured into water, and after several hours' stirring, the *product* was separated by decantation, dried in a vacuum, and crystallised from benzene–light petroleum (b. p. 40—60°) (yield, 39%); colourless needles, m. p. 128° (Found: C, 50·7; H, 5·8; N, 20·1; Cl, 12·4. $C_{12}H_{17}N_4ClS$ requires C, 50·6; H, 6·0; N, 19·7; Cl, 12·5%).

N^1-p-*Chlorophenyl*-N^3: N^4-*dimethyl*-N^5-iso*propyldiguanide* (II; R = Pr^i, R' = R'' = Me).—(*a*) *N*-(*N*-*p*-Chlorophenyl-*N'*-methylguanyl)-*N'*-*iso*propylthiourea hydrochloride (7 g.), mercuric oxide (10 g.), 21% aqueous methylamine (21 c.c.), and alcohol (50 c.c.) were stirred at 30—35° for 20 hours. The mixture was treated with dilute hydrochloric acid and sodium sulphide, filtered, and made alkaline with sodium hydroxide. The precipitated product was extracted with benzene, and the solution dried and evaporated. The residue remaining after evaporation of the benzene was dissolved in 2N-hydrochloric acid, and the solution filtered and neutralised with ammonia. Addition of salt precipitated the *hydrochloride* which was collected, washed with sodium chloride solution, then with water, and dried. Crystallised from alcohol–ethyl acetate it formed small colourless needles (3·1 g.), m. p. 177—178° (Found: C, 49·2; H, 6·4; N, 22·4; Cl, 22·6. $C_{13}H_{20}N_5Cl,HCl$ requires C, 49·1; H, 6·6; N, 22·0; Cl, 22·3%) (5731). With ammoniacal copper sulphate it gave a green copper complex soluble in benzene.

(*b*) *N*-*p*-Chlorophenyl-*N'*-(*N*-methyl-*N'*-*iso*propylguanyl)thiourea (1 g.), mercuric oxide (2 g.), 21% aqueous methylamine (5 c.c.), and alcohol (20 c.c.) were stirred at 30—35° for 23 hours, and the mixture worked up as in (*a*) to give the same product (0·55 g.), m. p. 176—177°, either alone or in admixture.

N-p-*Chlorophenyl*-N'-*ethylguanidine* (III; R = Cl, R' = Et).—*N*-*p*-Chlorophenyl-*S*-methyl*iso*thiourea (20 g.), 33% aqueous ethylamine (15 g.), and alcohol (20 c.c.) were heated at 80° for 4 hours in a closed vessel. The mixture was evaporated to dryness, and the residual gum dried by evaporation with benzene. The product could not be induced to crystallise, but it afforded a *picrate* which crystallised from alcohol as yellow prisms, m. p. 165° (Found: C, 42·8; H, 4·2; N, 20·5. $C_9H_{12}N_3Cl,C_6H_3O_7N_3$ requires C, 42·2; H, 3·5; N, 19·7%).

N-(N-p-*Chlorophenyl*-N'-*ethylguanyl*)-N'-iso*propylthiourea* (VIII; R = Pr^i, R' = Et).—The above crude guanidine (18 g.) and *iso*propyl *iso*thiocyanate (8·3 g.) were heated at steam-bath temperature for 6 hours, and then steam-distilled to remove unchanged *iso*thiocyanate. After cooling, the residual product was separated by decantation and crystallised from alcohol to give (VIII; R = Pr^i, R' = Et) as colourless prisms, m. p. 132—133° (Found: C, 52·3; H, 6·3; N, 19·0; Cl, 12·3. $C_{13}H_{19}N_4ClS$ requires C, 52·3; H, 6·4; N, 18·8; Cl, 11·9%).

Reaction of N-(N-p-*Chlorophenyl*-N'-*ethylguanyl*)-N'-iso*propylthiourea with Ammonia*.—The preceding compound (2 g.), mercuric oxide (4 g.), and alcoholic ammonia (25 c.c. of 13%) were stirred at room temperature for 20 hours and worked up to give the base as a non-crystallisable gum. This was dissolved in 2N-hydrochloric acid, and the solution neutralised with ammonia and treated with sodium chloride. The aqueous layer was decanted from the gummy precipitate which was dried by repeated evaporation of the solution in alcohol, followed by crystallisation from ethyl acetate to give N^1-*p*-chlorophenyl-N^3-ethyl-N^5-*iso*propyldiguanide hydrochloride, m. p. 174—176°, identical with the material described in Part XXIX.

N^1-p-*Chlorophenyl*-N^4-*methyl*-N^3-*ethyl*-N^5-iso*propyldiguanide* (II; R = Pr^i, R' = Me, R'' = Et).—*N*-(*N*-*p*-Chlorophenyl-*N'*-ethylguanyl)-*N'*-*iso*propylthiourea (5 g.), mercuric oxide (10 g.), and methylamine (15 c.c. of 21% aqueous solution) were kept at 30—35° in alcohol (50 c.c.) for 20 hours, and the mixture worked up to give a base which was dissolved in 2N-hydrochloric acid. The solution was neutralised with ammonia and saturated with sodium chloride; the precipitated *hydrochloride* crystallised on standing, and was collected, washed, dried, and crystallised from alcohol–ethyl acetate (yield, 2·2 g.). It formed tiny colourless rods, m. p. 152° (Found: C, 50·6; H, 6·8; N, 20·8; Cl, 21·0. $C_{14}H_{22}N_5Cl,HCl$ requires C, 50·6; H, 6·9; N, 21·1; Cl, 21·4%) (5757).

N^1-p-*Chlorophenyl*-N^3: N^4-*diethyl*-N^5-iso*propyldiguanide* (II; R = Pr^i, R' = R'' = Et).—Prepared similarly using ethylamine in place of methylamine, the *hydrochloride* could only be crystallised after dissolving it in alcohol and evaporating the solution to dryness several times. It then separated from ethyl acetate as tiny colourless rods, m. p. 145—146° (Found: C, 51·9; H, 6·9; N, 20·7; Cl, 20·7. $C_{15}H_{24}N_5Cl,HCl$ requires C, 52·0; H, 7·2; N, 20·2; Cl, 20·5%) (5758).

N-*Phenyl*-N'-p-*chlorophenylthiourea*.—A mixture of phenyl *iso*thiocyanate (16·1 g.) and *p*-chloroaniline (15·2 g.) was gradually heated to 100° and kept there for ½ hour. The cooled melt was ground and crystallised from alcohol to give the product (20·5 g.) as colourless plates, m. p. 156—158° (Found: C, 58·9; H, 4·2; N, 11·0. Calc. for $C_{13}H_{11}N_2ClS$: C, 59·4; H, 4·2; N, 10·7%). The same compound (m. p. and mixed m. p. 156—157°) was obtained from *p*-chlorophenyl *iso*thiocyanate and aniline (cf. Losanitsch, *Ber.*, 1872, **5**, 157, and Kjellin, *ibid.*, 1903, **36**, 197).

N-p-*Chlorophenyl*-N'-p-*tolylthiourea*.—Prepared similarly from *p*-chlorophenyl *iso*thiocyanate and *p*-toluidine, the *compound* crystallised from xylene as colourless plates, m. p. 174—175° (Found: C, 61·3; H, 4·7; N, 10·5. $C_{14}H_{13}N_2ClS$ requires C, 60·8; H, 4·7; N, 10·1%).

N-*Phenyl*-N'-p-*chlorophenylguanidine* (III; R = Cl, R' = Ph).—*N*-Phenyl-*N'*-*p*-chlorophenylthiourea (26·25 g.) and mercuric oxide (43·4 g.) were added to ice-cold saturated alcoholic ammonia (400 c.c.), and, with stirring, the temperature was gradually raised to 30°. After stirring at 30—35° overnight, the

mixture was raised to the boil to drive off excess of ammonia, then cooled and filtered. The filtrate was evaporated to dryness, and the residue crystallised from benzene to give the *product* (12·7 g.) as colourless prisms, m. p. 149—151° (Found: C, 64·1; H, 4·8; N, 17·1. $C_{13}H_{12}N_3Cl$ requires C, 63·5; H, 4·9; N, 17·1%).

N-p-*Chlorophenyl*-N′-p-*tolylguanidine* (III; R = Cl, R′ = *p*-C_6H_4Me).—Prepared from *N*-*p*-chlorophenyl-*N*′-*p*-tolylthiourea, this *compound* formed colourless long flat prisms from benzene, m. p. 148—150° (Found: N, 16·6. $C_{14}H_{14}N_3Cl$ requires N, 16·2%).

NN′-*Di*-p-*chlorophenylguanidine* (III; R = Cl, R′ = *p*-C_6H_4Cl).—Prepared analogously from *NN*′-di-*p*-chlorophenylthiourea, the compound was obtained as colourless fine needles by crystallisation from toluene, m. p. 146—147° (Losanitsch, *Bull. Soc. chim.*, 1879, **32**, 170, gives m. p. 140—141°).

N-(N-*Phenyl*-N′-p-*chlorophenylguanyl*)-N′-iso*propylthiourea* (VIII; R = Pr^i, R′ = Ph).—*N*-Phenyl-*N*′-*p*-chlorophenylguanidine (4·09 g.) and *iso*propyl *iso*thiocyanate (1·7 g.) were boiled in benzene (25 c.c.) for 5 hours. The benzene was evaporated and the residue extracted with boiling light petroleum (b. p. 100—120°). On cooling, the extract deposited a sticky solid which was further purified by crystallisation from alcohol to give (VIII; R = Pr^i, R′ = Ph), m. p. 133—135° (Found: C, 58·5; H, 5·5; N, 16·4; Cl, 10·4. $C_{17}H_{19}N_4ClS$ requires C, 58·9; H, 5·5; N, 16·2; Cl, 10·2%).

N-(N-p-*Chlorophenyl*-N′-p-*tolylguanyl*)-N′-iso*propylthiourea* (VIII; R = Pr^i, R′ = *p*-C_6H_4Me).—Similarly prepared from *iso*propyl *iso*thiocyanate and N-*p*-chlorophenyl-N′-*p*-tolylguanidine, this *compound* crystallised from light petroleum, m. p. 138—140° (Found: C, 60·2; H, 5·6; N, 15·2. $C_{18}H_{21}N_4ClS$ requires C, 59·9; H, 5·8; N, 15·5%).

N-(NN′-*Di*-p-*chlorophenylguanyl*)-N′-iso*propylthiourea* (VIII; R = Pr^i, R′ = *p*-C_6H_4Cl).—Prepared in a corresponding manner from *NN*′-di-*p*-chlorophenylguanidine and *iso*propyl *iso*thiocyanate and crystallised from benzene, this *compound* formed colourless long flat prisms, m. p. 154—156° (Found: C, 53·9; H, 4·8; N, 14·9; Cl, 18·7. $C_{17}H_{18}N_4Cl_2S$ requires C, 53·5; H, 4·7; N, 14·7; Cl, 18·6%).

N^1-*Phenyl*-N^3-p-*chlorophenyl*-N^5-iso*propyldiguanide* (II; R = Pr^i, R′ = H, R″ = Ph).—*N*-(*N*-Phenyl-*N*′-*p*-chlorophenylguanyl)-*N*′-*iso*propylthiourea (3·25 g.), mercuric oxide (4·34 g.), and saturated alcoholic ammonia (50 c.c.) were stirred at 40—45° overnight. The mixture was then filtered and the filtrate evaporated to dryness. The residue was dissolved in a warm mixture of acetic acid (30 c.c.) and water (70 c.c.), and the solution carbon-treated and filtered. Addition of sodium hydroxide to the filtrate precipitated the *acetate* which was collected, washed with water, and dried. Crystallised from chlorobenzene it formed colourless needles (1·5 g.), m. p. 170—172° (Found: C, 58·0; H, 6·2; N, 18·3. $C_{17}H_{20}N_5Cl,C_2H_4O_2$ requires C, 58·5; H, 6·2; N, 18·0%) (5604).

N^1-p-*Chlorophenyl*-N^3-p-*tolyl*-N^5-iso*propyldiguanide* (III; R = Pr^i, R′ = H, R″ = *p*-C_6H_4Me).—Similarly prepared from *N*-(*N*-*p*-chlorophenyl-*N*′-*p*-tolylguanyl)-*N*′-*iso*propylthiourea, the *acetate* crystallised from chlorobenzene as colourless blunt-ended needles, m. p. 174—176° (Found: C, 60·0; H, 6·6; N, 17·0. $C_{18}H_{22}N_5Cl,C_2H_4O_2$ requires C, 59·5; H, 6·4; N, 17·4%) (5605).

N^1 : N^3-*Di*-p-*chlorophenyl*-N^5-iso*propyldiguanide* (III; R = Pr^i, R′ = H, R″ = *p*-C_6H_4Cl).—Likewise prepared from N-(*NN*′-di-*p*-chlorophenylguanyl)-*N*′-*iso*propylthiourea, the *acetate* crystallised from chlorobenzene as colourless prisms, m. p. 176° (Found: C, 53·5; H, 5·6; Cl, 16·1. $C_{17}H_{19}N_5Cl_2,C_2H_4O_2$ requires C, 53·8; H, 5·4; Cl, 16·7%) (5603).

N^1 : N^3-*Di*-p-*chlorophenyl*-N^4-*ethyl*-N^5-iso*propyldiguanide* (III; R = Pr^i, R′ = Et, R″ = *p*-C_6H_4Cl).—*N*-(*NN*′-Di-*p*-chlorophenylguanyl)-*N*′-*iso*propylthiourea (6·35 g.), mercuric oxide (8 g.), ethylamine (12·1 g. of 31%), and alcohol (100 c.c.) were stirred at 30—35° for 16 hours, and the mixture then filtered. The filtrate was evaporated to dryness under reduced pressure and the residue dissolved in hot water (80 c.c.) and acetic acid (40 c.c.). The solution was carbon-treated, filtered, and added to sodium hydroxide to precipitate the product which was filtered off, washed with water, and dried. Crystallised from chlorobenzene, the *base* formed colourless long flat prisms, m. p. 167—169° (Found: C, 55·4; H, 6·2; N, 16·6; Cl, 16·9. $C_{19}H_{23}N_5Cl_2,H_2O$ requires C, 55·6; H, 6·1; N, 17·1; Cl, 17·3%) (5785).

N^1-p-*Chlorophenyl*-N^3 : N^3-*dimethyl*-N^5-iso*propyldiguanide* (IX; R = H, R′ = Pr^i, R″ = Me).—*N*-*p*-Chlorophenyl-*N*′-*iso*propylguanylthiourea (5 g.) (Part XXIX), mercuric oxide (5 g.), 2-ethoxyethanol (40 c.c.), and 25% aqueous dimethylamine (25 c.c.) were stirred for 6 hours at 55°. The mixture was diluted with acetone (100 c.c.) and filtered, and the filtrate evaporated. The residual base was converted into its *dihydrochloride* by dissolving it in alcoholic hydrogen chloride and adding ethyl acetate. This salt separated from alcohol–ethyl acetate as a colourless microcrystalline powder (4·15 g.), m. p. 191—193° (Found: C, 43·8; H, 6·1; N, 19·3; Cl, 30·0. $C_{13}H_{19}N_5Cl,2HCl$ requires C, 44·0; H, 6·2; N, 19·7; Cl, 30·0%) (5368).

N^1-p-*Chlorophenyl*-N^3 : N^3 : N^5 : N^5-*tetramethyldiguanide* (IX; R = R′ = R″ = Me).—*N*-*p*-Chlorophenyl-*N*′-(*NN*-dimethylguanyl)thiourea (6 g.) (Part XXIX), mercuric oxide (10 g.), alcohol (100 c.c.), and aqueous dimethylamine (30 c.c. of 25%) were stirred for 16 hours at 30—40°. Dilute hydrochloric acid was then added to render the mixture acid to Congo-red, followed by excess of sodium sulphide, and the whole was then filtered and made alkaline with sodium hydroxide. The base, isolated by extraction with benzene and evaporation of the dried benzene solution, was dissolved in 2N-hydrochloric acid, and the solution neutralised with ammonia and treated with a litttle sodium chloride. The precipitated *hydrochloride* crystallised on long standing and was collected, dried, and recrystallised from alcohol–ethyl acetate (yield, 1·85 g.); colourless rods, m. p. 212° (Found: C, 46·4; H, 6·9; Cl, 22·4. $C_{12}H_{18}N_5Cl,HCl,0{\cdot}5H_2O$ requires C, 46·0; H, 6·4; Cl, 22·7%) (5710).

N-p-*Chlorophenyl*-N′-*guanylthiourea* (VI; R = Cl, R′ = R″ = R‴ = H).—Sodium (1·5 g.) was dissolved in acetone (50 c.c.), and to the resulting sludge guanidine nitrate (8·8 g.) was added. After stirring for a short time, during which the mixture became more fluid, *p*-chlorophenyl *iso*thiocyanate (8·4 g.) was added with cooling. The mixture was then stirred for ½ hour at 30° and poured on ice (500 g.). The precipitated product was collected, washed with water, dried, and crystallised from methanol. Recrystallisation from xylene–butanol gave N-p-*chlorophenyl*-N′-*guanylthiourea* as colourless long thin prisms (yield, 43·5%), m. p. 195° (Found: C, 41·9; H, 4·0; N, 24·8; S, 13·9. $C_8H_9N_4ClS$ requires C, 42·0; H, 3·9; N, 24·5; S, 14·0%) (4588).

N^1-p-*Chlorophenyl*-N^2-iso*propyldiguanide* (II; R = R′ = H, R″ = Pr^i).—The preceding compound (9·2 g.), mercuric oxide (8·8 g.), and *iso*propylamine (6 c.c.) were shaken in a closed vessel overnight. The mixture was diluted with ether (50 c.c.) and filtered, and the ether evaporated. The residue was crystallised first from dilute alcohol and then from benzene–light petroleum (b. p. 60—80°) to give the *product* as colourless boat-shaped crystals, m. p. 166—168° (Found: C, 52·1; H, 6·2; N, 27·4. $C_{11}H_{16}N_5Cl$ requires C, 52·1; H, 6·3; N, 27·6%) (4765).

N^1-p-*Chlorophenyl*-N^2-n-*propyldiguanide* (II; R = R′ = H, R″ = Pr^n).—Prepared similarly using *n*-propylamine in place of *iso*propylamine, the *compound* was crystallised from benzene–light petroleum (b. p. 80—100°) and recrystallised from methyl*cyclo*hexane (yield, 45%); it was a colourless microcrystalline powder, m. p. 152·5—153·5° (Found: C, 51·7; H, 6·1; N, 14·2. $C_{11}H_{16}N_5Cl$ requires C, 52·1; H, 6·3; Cl, 14·0%) (4769).

N^1-p-*Chlorophenyl*-N^2 : N^2-*diethyldiguanide* (IX; R = R′ = H, R″ = Et).—Prepared analogously using diethylamine, the *product* crystallised from alcohol–light petroleum (b. p. 100—120°) as clusters of colourless needles, m. p. 174—175° (Found: C, 53·5; H, 7·0; Cl, 12·7. $C_{12}H_{18}N_5Cl$ requires C, 53·8; H, 6·7; Cl, 13·3%) (4766).

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[*Received April 21st*, 1948.]

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108. *The Cross-linking of Vinyl Polymers by Friedel–Crafts Catalysts. Part II.*

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The results of experiments on the Friedel–Crafts-catalysed cross-linking of various polymers, are discussed from the point of view of the electronic mechanisms of the reactions. The conclusions reached lend support to current theories of Friedel–Crafts reactions. It is shown that the cross-linking reaction probably involves unsaturated groupings in the polymer molecules, these groupings either being present normally in the polymer, or being introduced into it by the elimination of a simple molecule HX under the influence of the catalysts.

IN a previous paper (Part I, *J.*, 1948, 771), a new method of cross-linking vinyl polymers was described. Polymers, such as polyvinyl chloride and polyvinyl acetate, dissolved in liquids of fairly high dielectric constant, for example nitrobenzene and tetrachloroethane, were treated with aluminium chloride or other Friedel–Crafts catalysts, and a coloured insoluble product was obtained.

Possible over-all equations were given without specifying the actual mechanism of the reactions involved. Further consideration of the problem has led to conclusions concerning the electronic mechanisms of the processes and it is the purpose of this communication to discuss them. The ideas developed give support to current theories concerning simple Friedel–Crafts reactions.

EXPERIMENTAL.

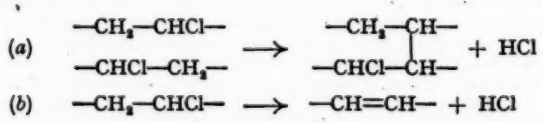
This paper is based on the observations recorded previously with the following additions:

(i) poly*iso*butene dissolved in tetrachloroethane and treated with aluminium chloride is not cross-linked; after chlorination, however, cross-linking can be introduced together with considerable darkening;

(ii) the cross-linked products formed from polyvinyl chloride, polyvinyl acetate, and polymethyl methacrylate, by the action of Friedel–Crafts catalysts, are not made soluble by treatment with dilute acids or alkalis.

DISCUSSION.

It was shown that besides introducing cross-linking into certain polymers, Friedel–Crafts catalysts can cause unsaturation to develop in these materials. The relevant equations written for polyvinyl chloride were:



(*a*) $\begin{matrix}-CH_2-CHCl- \\ -CHCl-CH_2-\end{matrix} \longrightarrow \begin{matrix}-CH_2-CH- \\ -CHCl-CH-\end{matrix}$ + HCl

(*b*) $-CH_2-CHCl- \longrightarrow -CH=CH-$ + HCl

It is generally accepted that when saturated hydrocarbons are involved in Friedel–Crafts reactions, unsaturation must be developed in them before reaction can occur (see, for example, Linstead, *Ann. Reports*, 1937, **34**, 251). It seems, therefore, that the two processes indicated above, are not completely separate and that the introduction of unsaturation may be an essential precursor to the formation of cross-linkages.

Fairbrother's work (*J.*, 1937, 503; *J.*, 1941, 293) showed that in a reaction involving an

alkyl chloride, a hydrocarbon, and aluminium chloride, the primary step does not involve the hydrocarbon and can be represented as

$$R{\cdot}Cl + AlCl_3 \rightleftharpoons R^+ + [AlCl_4]^-$$

Taking polyvinyl chloride as the alkyl chloride, the equation $\cdot CH_2{\cdot}CHCl\cdot + AlCl_3 \rightleftharpoons \cdot CH_2{\cdot}\overset{+}{C}H\cdot + [AlCl_4]^-$ can be written. The loss of a proton from the carbonium ion thus:

$$\cdot CH_2{\cdot}\overset{+}{C}H\cdot \longrightarrow \cdot CH{:}CH\cdot + H^+$$

would lead to unsaturation and to the possibility of colour (see, for example, Bowen, *Ann. Reports*, 1943, **40**, 12).

Further evidence for this mechanism is provided by kinetic studies of the formation of olefins by the action of alkalis on certain alkyl halides (Hughes, Ingold, Masterman, and McNulty, *J.*, 1940, 899). The ionisation $H{\cdot}CR_2{\cdot}CR_2{\cdot}X \longrightarrow H{\cdot}CR_2{\cdot}\overset{+}{C}R_2 + X^-$ is thought to be followed by the step $H{\cdot}CR_2{\cdot}\overset{+}{C}R_2 \longrightarrow CR_2{:}CR_2 + H^+$ similar to the second stage in the scheme proposed above.

The bromination of alkyl bromides in the presence of ferric bromide leads to the substitution of a bromine atom on the carbon atom adjacent to the one already carrying a bromine atom (see Gilman, "Organic Chemistry", Wiley, New York, 2nd Edition, 1943, p. 180). This observation was explained by supposing that first the ferric bromide introduces unsaturation into the alkyl halide (as postulated above for polyvinyl chloride), $R{\cdot}CH_2{\cdot}CH_2Br \longrightarrow R{\cdot}CH{:}CH_2 + HBr$, and that bromine then adds across the double bond.

As mentioned already, when saturated hydrocarbons are involved in Friedel–Crafts reactions unsaturation must be developed in them before reaction can occur. It has been suggested that the double bond is involved in the formation of an unstable complex. In the case of polyvinyl chloride such unsaturation is developed and the mechanism proposed to explain its appearance is both simple and reasonable. The complex can be considered as resulting from the donation of electrons from a carbon atom to the electrophilic catalyst, thus

$$\begin{array}{c} -CH{=}CH- \\ \downarrow \\ AlCl_3 \end{array}$$

There would be a marked tendency for such a complex to lose a proton in its reactions because electrons would be drawn away from a carbon–hydrogen bond, and it would effectively react as a negative grouping $\cdot CH{:}\overset{-}{C}$. If the complex interacts with the positive ion already described, cross-linking could occur by the reaction

$$\begin{array}{l} \cdot CH_2{\cdot}\overset{+}{C}H\cdot \\ \cdot CH{:}CH\cdot \\ (AlCl_3) \end{array} \longrightarrow \begin{array}{l} \cdot CH_2{\cdot}CH\cdot \\ \quad\vert \\ \cdot CH{:}C\cdot \end{array} + H^+ + AlCl_3$$

The dependence of the speed of the whole reaction upon the dielectric constant of the solvent was described previously (Part I, *loc. cit.*). The effect is attributed in the main to the dependence of the primary formation of the positive ion on the dielectric constant; that process, involving the separation of oppositely charged entities, would be favoured in media of high dielectric constant where the electrostatic attraction between the charged bodies would be small. Subsequent steps in the sequence of reactions leading to cross-linking do not involve actual separation of charges, and are therefore likely not to be markedly affected by dielectric constant.

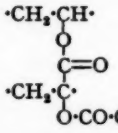
The equations developed to explain the cross-linking of polyvinyl chloride can equally well be applied to the other chlorine-containing polymers studied *viz.*, chlorinated polyvinyl chloride, halothene, chlorinated poly*iso*butene, and co-polymers containing vinyl chloride.

In the case of polyvinyl acetate, the preliminary ionisation is represented as:

$$\cdot CH_2{\cdot}CH(O{\cdot}CO{\cdot}CH_3)\cdot + AlCl_3 \rightleftharpoons \cdot CH_2{\cdot}\overset{+}{C}H\cdot + [CH_3{\cdot}CO_2{\cdot}AlCl_3]^-$$

being followed by the ejection of proton to give $\cdot CH{:}CH\cdot$. Subsequent reactions of the olefinic group and the positive ion can be formulated in the same manner as in the case of polymers containing chlorine. The cross-linkage is not of the type present in the product of the photochemical polymerisation of the vapour of vinyl acetate (Melville and Tuckett, *J.*, 1947, 1201);

that product is made soluble in water by treatment with potassium hydroxide and its structure is probably :



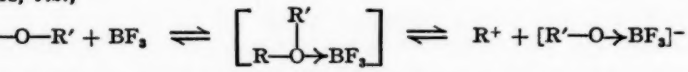
The resistance of the material formed by Friedel–Crafts catalysts to the action of acids and alkalis shows that it does not contain cross-linkages easily cleaved by hydrolysing agents, and that the separate polymer molecules are linked by carbon–carbon bonds.

The primary step in the cross-linking of polymers of *n*-butyl vinyl ether is written as

$$\cdot CH_2 \cdot CH(O \cdot C_4H_9) \cdot + AlCl_3 \rightleftharpoons \cdot CH_2 \cdot \overset{+}{C}H \cdot + [C_4H_9 \cdot O \cdot AlCl_3]^-$$

followed by the formation of olefinic groupings, which would account for the darkening observed when polymerising the monomer with Friedel–Crafts catalysts (Chalmers, *Canadian J. Res.*, 1932, **7**, 472). Cross-linking is developed by the interaction of the carbonium ion and the olefinic grouping in the manner described already.

The equations given for the initial ionisation of polyvinyl acetate and polyvinyl ether are analogous with the general equation proposed by Price and Ciskowski (*J. Amer. Chem. Soc.*, 1938, **60**, 2499) to represent the primary step in Friedel–Crafts reactions involving alcohols, esters, and ethers, *viz.*,



where R′ can be a hydrogen atom, an acyl group, or an alkyl group.

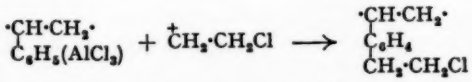
Polystyrene cannot be cross-linked in nitrobenzene solution because the polymer does not contain reactive groups, the removal of which would yield positive ions. The polymer can be cross-linked in solvents containing more than one chlorine atom per molecule, presumably by a composite reaction involving the solvent.

Taking ethylene dichloride as the solvent, it is visualised that cross-limking takes place by the following series of reactions :

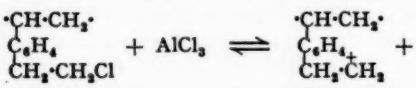
(i) the formation of a positive ion from a molecule of solvent :

$$Cl \cdot CH_2 \cdot CH_2 \cdot Cl + AlCl_3 \rightleftharpoons Cl \cdot CH_2 \cdot \overset{+}{C}H_2 + [AlCl_4]^-;$$

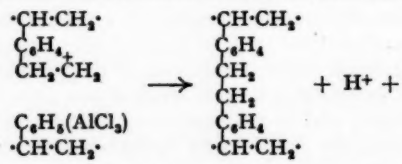
(ii) the substitution of the chloroethyl group into the phenyl group of a polymer, by the interaction of the positive ions shown in (i) with the complex formed between the catalyst and the polymer :



(iii) ionisation of the substituted polymer formed in (ii), under the influence of the catalyst :



(iv) this ionised polymer molecule reacts with a polymer–catalyst complex as shown in (ii) :



Fairbrother showed (*J.*, 1941, 293) that the carbon–halogen bonds in halogenated benzenes show no tendency to undergo heteropolar fission according to the scheme :

$$C_6H_5 \cdot X + AlCl_3 \rightleftharpoons C_6H_5^+ + [AlCl_3X]^-;$$

consequently polystyrenes chlorinated in benzene rings would behave, from the point of view of Friedel–Crafts-catalysed cross-linking, just as unsubstituted polystyrene. Polymers of

α- or β-chlorostyrene would be expected to undergo cross-linking in nitrobenzene, because the preliminary ionisation

$$\cdot CH(C_6H_5)\cdot CHCl\cdot + AlCl_3 \rightleftharpoons \cdot CH(C_6H_5)\cdot \overset{+}{C}H\cdot + [AlCl_4]^-$$

can occur. The phenomenon is actually observed. Cross-linking could take place according to two equations; in the first, the positive ion reacts with a complex of aluminium chloride and a phenyl group in the polymer. In the second equation cross-linking results from the interaction of the positive ion with a complex involving a double bond in the straight chain of the polymer, as in the case of polyvinyl chloride:

(i)
$$\begin{array}{l}\cdot CH(C_6H_5)\cdot \overset{+}{C}H\cdot \\ \qquad\quad C_6H_5(AlCl_3) \\ \cdot CH_2\cdot CH\cdot\end{array} \longrightarrow \begin{array}{l}\cdot CH(C_6H_5)\cdot CH\cdot \\ \qquad\quad C_6H_4 \\ \cdot CH_2\cdot CH\cdot\end{array} + H^+ + AlCl_3$$

(ii)
$$\begin{array}{l}\cdot CH(C_6H_5)\cdot \overset{+}{C}H\cdot \\ \cdot C(C_6H_5){:}CH\cdot \\ \qquad (AlCl_3)\end{array} \longrightarrow \begin{array}{l}\cdot CH(C_6H_5)\cdot CH\cdot \\ \cdot C(C_6H_5){:}C\cdot\end{array} + H^+ + AlCl_3.$$

Even in suitable chlorinated solvents, cross-linking can occur only if (i) the polymer normally contains double bonds (as in polymers containing the benzene nucleus), or (ii) if unsaturation can be induced in it by the two-stage elimination of a fairly simple molecule HX. Unlike polystyrene, another hydrocarbon polymer, poly*iso*butene, cannot be cross-linked even when dissolved in tetrachloroethane, because it cannot satisfy either of the conditions given above.

As reported before, polymethyl methacrylate is cross-linked with only slight accompanying discolouration, which suggests that little, if any, unsaturation is introduced during treatment with Friedel–Crafts catalysts. Consequently the mechanism shown below, involving steps analogous with those proposed for the case of polyvinyl chloride, is rejected:

(i)
$$\cdot CH_2\cdot \begin{array}{l}C(CH_3)\cdot \\ CO_2CH_3\end{array} + AlCl_3 \rightleftharpoons \cdot CH_2\cdot \overset{+}{C}(CH_3)\cdot + [AlCl_3\cdot CO_2CH_3]^-$$

(ii)
$$\cdot CH_2\cdot \overset{+}{C}(CH_3)\cdot \longrightarrow \cdot CH{:}C(CH_3)\cdot + H^+$$

(iii)
$$\begin{array}{l}\cdot CH_2\cdot \overset{+}{C}(CH_3)\cdot \\ \cdot C(CH_3){:}CH\cdot \\ \qquad (AlCl_3)\end{array} \longrightarrow \begin{array}{l}\cdot CH_2\cdot C(CH_3)\cdot \\ \cdot C(CH_3){:}C\cdot\end{array} + H^+ + AlCl_3$$

Various *ad hoc* hypotheses can be made about the mechanism of the reaction; for example it seems feasible that if the carbonyl group donates electrons to the catalyst, it would be unnecessary to introduce further unsaturation into the molecule. The over-all equation could therefore be

$$\begin{array}{l}\cdot CH_2\cdot \begin{array}{l}C(CH_3)\cdot \\ CO_2CH_3\end{array} \\ \cdot \begin{array}{l}C(CH_3)\cdot CH_2\cdot \\ CO_2CH_3\end{array}\end{array} \xrightarrow{AlCl_3} \begin{array}{l}\cdot CH_2\cdot C(CH_3)\cdot \\ \qquad\quad C{:}O \\ \cdot C(CH_3)\cdot CH\cdot \\ \qquad CO_2CH_3\end{array} + CH_3\cdot OH$$

giving a cross-linkage stable to acids and alkalis, as observed.*

The work described here was performed during the tenure by the junior author of a Research Fellowship at Queen's College, Cambridge.

Department of Physical Chemistry, Cambridge. [*Received, May* 12th, 1948.]

* *Added in Proof.*—We are grateful to Dr. E. H. Farmer for pointing out that the group $\cdot CH{:}CH\cdot CH_2\cdot$ is more likely to react as $\cdot CH{:}CH\cdot \bar{C}H\cdot$ or $\cdot \bar{C}H\cdot CH{:}CH\cdot$ than as $\cdot CH{:}\bar{C}\cdot CH_2\cdot$. The overall equation for the final step in the cross-linking of polyvinyl chloride should therefore be written:

$$\begin{array}{l}\cdot CH_2\cdot \overset{+}{C}H\cdot \\ \cdot CH{:}CH\cdot CH_2\cdot\end{array} \longrightarrow \begin{array}{l}\cdot CH_2\cdot CH\cdot \\ \cdot CH{:}CH\cdot CH\cdot\end{array} + H^+$$

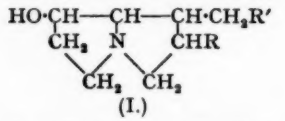
This reaction may depend upon the formation of a complex between the olefinic group and the catalyst as suggested above, or alternatively it might occur without the participation of a catalyst molecule. In the second case, the reaction would be similar to that proposed for the primary formation of the olefinic group, with the ejection of the proton occurring intermolecularly instead of intramolecularly; the catalyst would be involved only once in the whole process of cross-linking. Slight revision is necessary in the equations proposed to explain the cross-linking of other polymers; the cross-linkage should be shown as involving a carbon atom adjacent to the group $\cdot CH{:}CH\cdot$ and not an atom of the group itself.

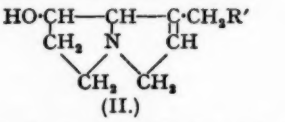
109. *The* Senecio *Alkaloids. Part II. Isatinecine.*

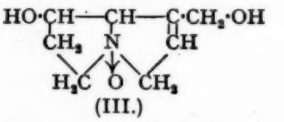
By Ernest C. Leisegang and Frank L. Warren.

Isatinecine, $C_8H_{13}O_3N$, is shown to be retronecine *N*-oxide. Catalytic reduction in the presence of Adams's catalyst gives retronecanol, $C_8H_{15}ON$, and with Raney nickel yields platynecine, $C_8H_{15}O_2N$. Isatinecine is reduced by zinc dust to retronecine, $C_8H_{13}O_2N$, which is oxidised by hydrogen peroxide to isatinecine.

Isatinecine, $C_8H_{13}O_3N$, obtained by hydrolysis of isatidine (Blackie, *Pharm. J.*, 1937, **138**, 1), has two hydrogen atoms less than rosmarinecine for which a constitution (I; R = R′ = OH) was suggested by Richardson and Warren (*J.*, 1943, 452).


(I.)


(II.)


(III.)

Isatidine on reduction absorbed four molecules of hydrogen to give octahydroanhydroisatidine which on hydrolysis gave tetrahydroisatinecine, $C_8H_{17}O_3N$ (de Waal, *Onderstepoort J. Vet. Sci. and Animal Husb.*, 1940, **14**, 433). From this, de Waal concluded that the pyrrolizidine nucleus, common to the other alkaloids of the *Senecio* species, was open, and suggested a 2-butenylpyrroline as the basic structure (*idem, ibid.*, 1941, **16**, 149; *Tydskrif vir Wetenskap en Kuns*, 1941, **1**, 88). All attempts to prepare derivatives to characterise the oxygen atoms failed to give any crystalline product and usually resulted in complete degradation. It was thought that the reduced molecule might be more stable, and reduction experiments were carried out. Catalytic reduction in the presence of Adams's catalyst in alcohol resulted in the absorption of three molecules of hydrogen to give a brown oil which had a strong odour of acetamide and from which a small quantity of crystalline material could be obtained by high-vacuum distillation. When reduction was effected in acid solution, exactly three molecules of hydrogen were taken up to give a colourless oil which sublimed completely in high vacuum to give crystals of retronecanol (I; R = R′ = H), which showed no depression in m. p. on admixture with an authentic specimen obtained by the hydrogenation of retronecine as described by Adams and Rogers (*J. Amer. Chem. Soc.*, 1939, **61**, 2815). That no change had occurred during distillation was established by the preparation of the picrate of the oily hydrogenation product which was identical with that of retronecanol.

The removal of one of the oxygen atoms during hydrogenation could be accounted for by the assumption of a retronecine structure (II; R′ = OH). This concept was supported by the reduction of isatinecine in the presence of Raney nickel, using the conditions of Adams and Rogers (*ibid.*, 1941, **64**, 540) for the reduction of retronecine; two molecules of hydrogen were smoothly absorbed to give a quantitative yield of platynecine (I; R = H, R′ = OH).

The elimination of the other oxygen atom during catalytic reduction could be explained by assuming the presence of either a tertiary amine-oxide grouping or an anionotropic system similar to that in cotarnine. A carbinol-amine grouping would not seem to be present in the free base, as this forms neither a nitromethane condensation product (cf. Hope and Robinson, *J.*, 1911, **99**, 2119) nor *O*-alkyl compounds when heated with alcohols (cf. Blount and Robinson, *J.*, 1932, 2305). To test the assumption of the presence of a tertiary nitrogen-oxide group, isatinecine was treated with zinc dust and dilute sulphuric acid; retronecine (II; R′ = OH) was quantitatively formed (cf. Dunstan, *J.*, 1899, **75**, 796). It would seem therefore that isatinecine is retronecine *N*-oxide (III), a structure which receives support by the ready oxidation with hydrogen peroxide (cf. *idem, ibid.*, p. 1004) of retronecine to isatinecine, obtained as a hygroscopic material but rendered anhydrous by boiling with alcohol (cf. hydrohydrastinene *N*-oxide prepared by Polonovski and Polonovski, *Bull. Soc. chim.*, 1936, **3**, 885).

Isatidine crystallises with two firmly bound molecules of water of crystallisation, a property associated with amine oxides, and attempts to dehydrate it over phosphoric oxide in a vacuum resulted in decomposition (de Waal, *Onderstepoort J. Vet. Sci. and Animal Husb.*, 1939, **12**, 159). Furthermore, both isatidine and isatinecine liberate iodine from potassium iodide in acetic acid on warming, which is a reaction reported by Hasse and Wolffenstein (*Ber.*, 1898, **31**, 1553) for *N*-alkylpiperidine *N*-oxides.

Experimental.

Isatinecine.—(*a*) Isatidine (3·76 g.; 1 mol.) in hot water (20 ml.) was added to barium hydroxide octahydrate (3·6 g.; 1·1 mols.) in water (30 ml.), and the mixture heated on a steam-bath for 2 hours.

Carbon dioxide was then passed into the boiling solution, and the barium carbonate was filtered off and washed with hot water. The combined filtrates were evaporated under reduced pressure at 40°, and the residue extracted with boiling absolute alcohol to leave barium isatinecate. The alcoholic filtrates, evaporated under reduced pressure, gave an almost quantitative yield of isatinecine, m. p. 214—215° (corr.) (decomp.) (Found: C, 55·8; H, 7·88; N, 8·22. Calc. for $C_8H_{13}O_3N$: C, 56·1; H, 7·65; N, 8·18%). de Waal (*Onderstepoort J. Vet. Sci.*, 1940, **14**, 441) gives m. p. 212—215°. The *picrate* crystallised from alcohol in rods, m. p. 145° (corr.) (Found: C, 42·1; H, 4·27. $C_{14}H_{16}O_{10}N_4$ requires C, 42·0; H, 4·03%).

(*b*) Retronecine (0·47 g.; 1 mol.) in alcohol was warmed with 30% hydrogen peroxide solution (0·50 ml.; 1·1 mols.) for 45 minutes. The solution on evaporation gave an oil which solidified on addition of dry acetone. The hygroscopic crystals were washed with dry acetone and dissolved in boiling alcohol (absolute), and the solvent was removed by evaporation. In a vacuum, the oil slowly set to a mass of crystals characteristic of isatinecine, m. p. 214° (corr.) (decomp.).

Retronecanol.—Isatinecine (2·83 g.; 1 mol.), neutralised with 4·6N-sulphuric acid (3·8 ml.) and diluted with water (300 ml.), was shaken with hydrogen and platinum (from 100 mg. of PtO_2). The hydrogen was slowly absorbed and the reaction was complete after 13 hours (observed 1·17 l. at S.T.P. Calc. for $C_8H_{13}O_3N$ for 3 $\overline{|}$: 1·11 l.). The solution was filtered, excess of barium hydroxide added to the hot filtrate, the excess precipitated by passing carbon dioxide, and the filtered solution evaporated to dryness under reduced pressure. The colourless viscous oil sublimed completely at 45—55°/0·001 mm. to give hygroscopic rhombic crystals, m. p. 92—94° (corr.) (Found: N, 10·0. Calc. for $C_8H_{15}ON$: N, 9·92%), undepressed by mixing with an authentic specimen obtained by hydrogenolysis of retrorsine according to the method of Adams and Rogers (*loc. cit.*). The picrate, from absolute alcohol, had m. p. 211—214° (corr.) (Found: C, 45·5; H, 4·61. Calc. for $C_{14}H_{18}O_8N_4$: C, 45·4; H, 4·90%).

Platynecine.—Isatinecine (4·59 g.) was shaken with hydrogen and Raney nickel (1·0 g., prepared according to the method of Colvert and Adkins, *J. Amer. Chem. Soc.*, 1932, **54**, 4117); the absorption was complete in 13 hours (observed 1·10 l. at S.T.P.; calc. for $C_8H_{13}O_3N$ for 2 $\overline{|}$: 1·20 l.). The solution was filtered and evaporated under reduced pressure to give a colourless viscous oil which crystallised immediately from acetone. Three crystallisations gave platynecine as colourless needles, m. p. 145—147° (corr.) (Found: N, 8·91. Calc. for $C_8H_{15}O_2N$: N, 8·91%), undepressed on admixture with an authentic specimen (Richardson and Warren, *J.*, 1943, 453). The picrate, from alcohol, had m. p. 183·5—185·5° (corr.). Orechov (*Ber.*, 1935, **68**, 1886) gives platynecine, m. p. 148—149·5°, and picrate, m. p. 184—185°.

Retronecine.—Isatinecine (0·5 g.; 1 mol.) was dissolved in 4·6N-sulphuric acid (10 ml.; 8 mols.) and water (25 ml.), and zinc dust (1·0 g.; 5 atoms) was added slowly. The reaction was completed by heating on a steam-bath until all the zinc had dissolved; powdered barium carbonate was then added in slight excess. The solution was filtered, the precipitate washed with hot alcohol, and the combined filtrates evaporated under reduced pressure. The residual oil crystallised from acetone to give retronecine as prisms, m. p. 121° (corr.) (Found: N, 9·2. Calc. for $C_8H_{13}O_3N$: N, 9·03%), undepressed by an authentic specimen obtained by hydrolysis of retrorsine according to the method of Barger, Seshadri, Watt, and Yabuta (*J.*, 1935, 11) who give m. p. 121—122°.

The authors acknowledge a grant from the National Research Council for the purchase of an extractor.

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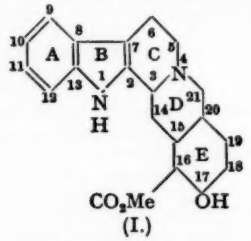
110. *The Constitution of Yohimbine. Part II.*

By G. R. CLEMO and G. A. SWAN.

The structure (II) suggested by Witkop for ketoyobyrine is disproved by synthesis. A synthesis of ketoyobyrine is described; this compound probably has structure (V), the only slight doubt being with regard to the double bond at C_5–C_6 and the single bond at C_3–C_{14}. This is regarded as being strong evidence for the location of the carbomethoxy-group at C_{16} in the yohimbine molecule.

ON dehydrogenation with selenium for 30 minutes at 300°, the alkaloid yohimbine gives rise to the basic compounds yobyrine and " tetrahydroyobyrine ", together with a smaller amount of ketoyobyrine, $C_{20}H_{16}ON_2$ (for references, see Part I, Clemo and Swan, *J.*, 1946, 617). The work described in Part I not only proved synthetically the constitution of yobyrine to be 2-(α-methylbenzyl)-β-carboline; but also demonstrated the possibility of formation of this compound from the ring-structure of yohimbine (probably I) by dehydrogenation, involving fission at the C_{21}–N_4 bond to enable ring C to aromatise. The synthesis of yobyrine (by a method almost identical with one of those mentioned above) has since been described by Julian, Karpel, Magnani, and Meyer (*J. Amer. Chem. Soc.*, 1948, **70**, 180), who have also synthesised " tetrahydroyobyrine ", which is formed by fission at the C_5–N_4 bond, enabling ring D to aromatise. The present communication deals with the structure of ketoyobyrine, which is of considerable importance, since it contains the carbonyl group derived from the carbomethoxy-group of the alkaloid; and hence the establishment of its structure can be taken as evidence for the location of the latter group.

Ketoyobyrine has been described as a bright yellow, crystalline solid, m. p. 330°, insoluble in dilute aqueous acids and alkalis. It is soluble in concentrated sulphuric acid, giving a red



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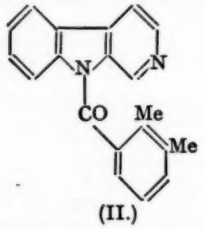
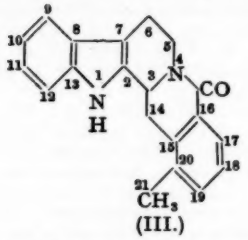


(II.)



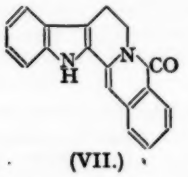
(III.)

(IV.) As III, but double bond at C_3–C_{14}. (V.) As III, but double bond at C_5–C_6.
(VI.) As III, but double bonds at C_3–C_{14} and C_5–C_6.

solution, but is reprecipitated on addition of water. It is slightly soluble in glacial acetic acid and in alcohol, giving yellow solutions, exhibiting a characteristic bluish-green fluorescence. By fission of ketoyobyrine with potassium hydroxide in amyl alcohol, Barger and Scholz (*Helv. Chim. Acta*, **1933**, **16**, 1343) obtained β-carboline and 2 : 3-dimethylbenzoic acid. As Mendlik and Wibaut (*Rec. Trav. chim.*, **1931**, **50**, 91) reported that dehydrogenation of diacetylyohimbine gave rise to yobyrine and " tetrahydroyobyrine ", but no ketoyobyrine, Barger and Scholz suggested that in the latter compound the carbonyl residue of the yohimbine carbomethoxy-group has become attached to N_1. Later, Witkop (*Annalen*, **1943**, **554**, 83) suggested structure (II) for ketoyobyrine. Clearly, these suggestions fail to explain the absence of basic properties in the compound; and, moreover, Raymond-Hamet (*Compt. rend.*, **1945**, **221**, 387) has pointed out the great difference in the ultra-violet absorption spectra of harman and ketoyobyrine. The condensation of β-carboline with 2 : 3-dimethylbenzoyl chloride, giving 1-(2 : 3-*dimethylbenzoyl*)-β-*carboline* (II), has now been carried out; the product was a colourless, crystalline solid, m. p. 151—153°, with the expected basic properties, and giving a blue fluorescence in acid solution.

A possible mode of formation of ketoyobyrine might be as follows. During the selenium dehydrogenation, bond C_{21}–N_4 is known to break in some yohimbine molecules; and this is usually followed by aromatisation of rings C and E, the hydroxyl and carbomethoxy-substituents being lost, and hence the main product here is yobyrine. But if, after the C_{21}–N_4 bond has broken, free rotation about the C_{14}–C_{15} bond should bring the carbomethoxy-group into the vicinity of N_4 before aromatisation of ring C had occurred, then cyclisation might occur to give structure (III), in which the atoms are given the same numbers as in (I), *e.g.*, the CH_3 group of (III) is derived from C_{21} of (I); (III) might then lose two or four hydrogen atoms with the formation of (IV), (V), or (VI). Either structure (IV) or (V) would appear possible for ketoyobyrine, and would explain the absence of basic properties.

In Part I were described preliminary experiments towards the synthesis of such a ring system. Condensation of tryptamine with homophthalic anhydride, esterification, and



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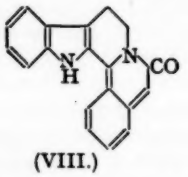

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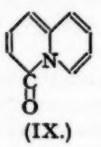
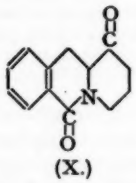
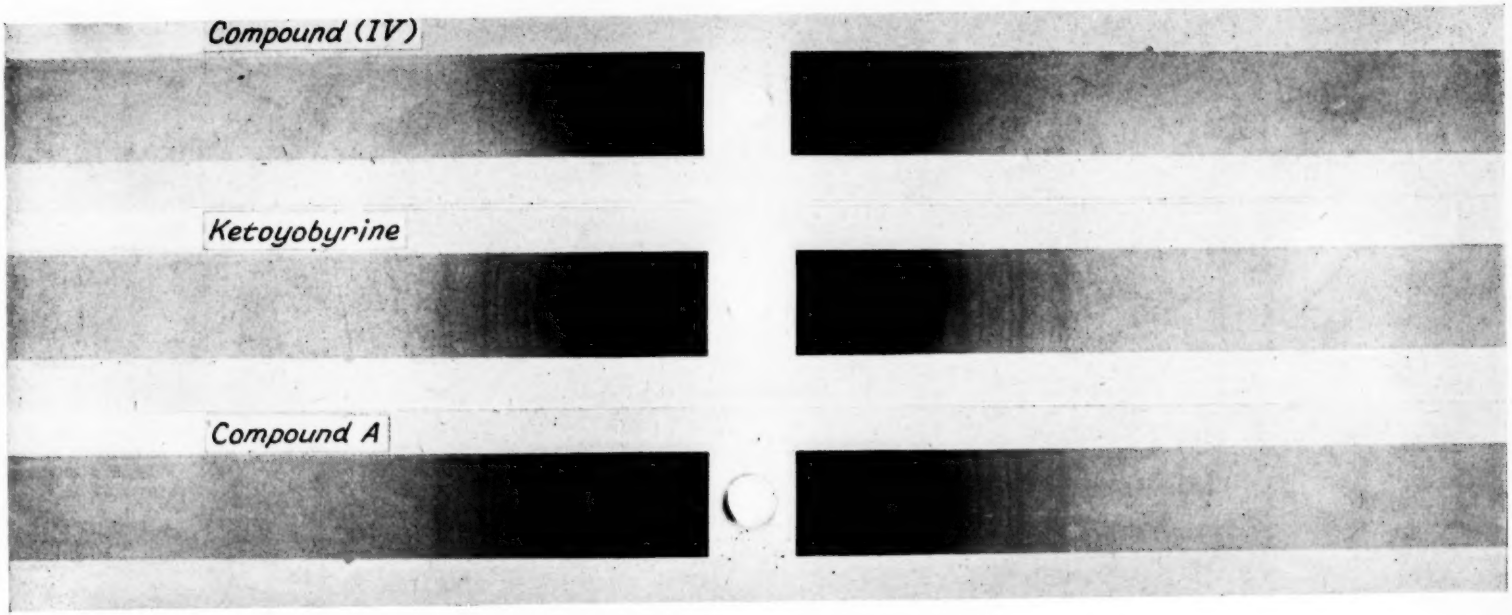


(IX.)



(X.)

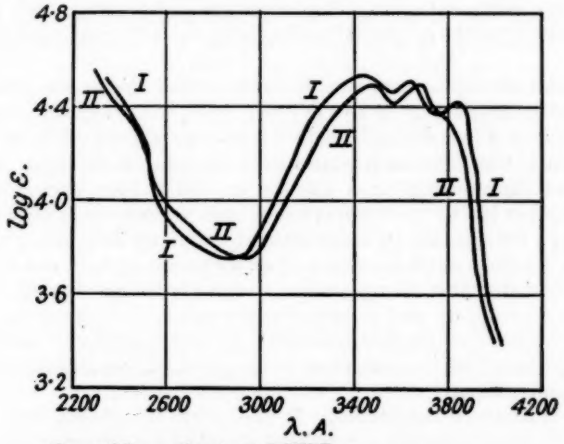
cyclisation of the product, led to formation of a trace of a pale yellow, crystalline compound, m. p. 299° (decomp.), which it was suggested might be 6-keto-7 : 8-benzo-1 : 2-(2′ : 3′-indolo)-3 : 4-dihydropyridocoline (VII). Recently, Schlittler and Allemann (*Helv. Chim. Acta*, **1948**, **31**, 128) have repeated this work and improved the yield obtained. In the experimental section of this paper are described conditions for still further improving the yield, and, moreover, the intermediate *methyl* N-(β-*indolylethyl*)*homophthalamate* was obtained as a crystalline solid (in contrast to the Swiss workers, who obtained only an oil). There was also the possibility that the condensation and cyclisation might have given rise to (VIII) instead of (VII) and, although this seemed unlikely in view of the pale yellow colour of the product (cf. oxyprotoberberine and oxy*iso*protoberberine; Haworth, Perkin, and Pink, *J.*, **1925**, **127**, 1709), further evidence on



[To face p. 489.

this point was sought. Attempts to carry out a quantitative catalytic hydrogenation were unsatisfactory, on account of the low solubility of the material in glacial acetic acid and alcohol; but the indication was that hydrogen uptake was very slow in the presence of platinum at room temperature and pressure. However, evidence in favour of structure (VII) was found in the fission with potassium hydroxide in amyl alcohol, which gave rise to *o*-toluic acid (in almost quantitative yield equivalent to the material decomposed) and a small amount of β-carboline.

The ultra-violet absorption spectra of (VII) and of ketoyobyrine in ethanol are shown in Curves I and II, respectively, and these bear a striking resemblance. But equally striking is the difference in the appearance of solution of these two compounds in the same solvent, the former being almost colourless, with a blue fluorescence, while the latter is yellow with a bluish-green fluorescence. (VII) is soluble in concentrated sulphuric acid, giving a yellow solution. However, it was found that when a solution of (VII) in xylene was boiled with Raney nickel and then allowed to cool, it deposited bright yellow crystals of a *compound* which appeared to be isomeric with (VII), but which differed from it in the appearance, colour, and optical properties of the crystals, in the appearance of the solution, which was yellow with a green fluorescence, and in giving a red solution in concentrated sulphuric acid.



Curve (I). *Compound (VII).*
Curve (II). *Compounds (IV), A, and ketoyobyrine.*

The synthesis of (IV) was then carried out. For this, 6-methylhomophthalic acid was required. This had previously been obtained by Mercer and Robertson (*J.*, 1936, 292) by condensation of *o*-toluoyl chloride with malonic ester, followed by reductive hydrolysis to give *o*-tolylpropionic acid, cyclisation of the chloride of which gave the methylindanone, which was converted into the homophthalic acid *via* the oximino-derivative. Repetition of this synthesis gave satisfactory yields except for the reductive hydrolysis, which was found to yield mainly *o*-toluic acid; and it was found preferable to prepare *o*-tolylpropionic acid from *o*-xylyl bromide, by condensation with malonic ester, followed by hydrolysis and decarboxylation. 6-Methylhomophthalic anhydride was condensed with tryptamine, and the product esterified with diazomethane giving *methyl* N-(β-*indolylethyl*)-6-*methylhomophthalamate*; this was cyclised with phosphoryl chloride, giving 6-*keto*-7 : 8-[1′ : 2′-(3′-*methylbenzo*)]-1 : 2-(2′ : 3′-*indolo*)-3 : 4-*dihydropyridocoline* (IV), a pale yellow crystalline solid, m. p. *ca.* 320° (decomp.), giving in alcoholic solution (2 mg./100 c.c.) an almost colourless solution with a blue fluorescence, and soluble in concentrated sulphuric acid to give a yellow solution, but whose ultra-violet absorption spectrum was indistinguishable from that of ketoyobyrine (Curve II). When (IV) was boiled in xylene solution with Raney nickel, it was converted into a bright yellow crystalline *compound A*, indistinguishable from ketoyobyrine in the crystalline state (under the microscope) or in solution (ultra-violet absorption spectrum, colour, and fluorescence) and in the colour of its solution in concentrated sulphuric acid. Mr. H. E. Blayden kindly arranged to photograph the *X*-ray diffraction patterns by the powder method in the Northern Coke Research Committee's Laboratory, Department of Physical Chemistry, King's College, Newcastle-upon-Tyne, and the results are shown on the accompanying Plate. The photographs from A and ketoyobyrine are indistinguishable; that of (IV) is very similar, but the outer lines are here absent, and some of

the others are of slightly different intensity. The samples were examined after the *X*-ray analysis and appeared to be unchanged by the treatment. The melting points of these materials appeared to be of little value for identification, as they varied with the rate of heating and were accompanied by decomposition and sublimation; however, the values determined for the synthetic and the degradative material were both *ca.* 322°, and admixture appeared not to cause depression.

From the above synthesis, the structure of (IV) appears well established. There remains to consider in what way A differs from this, and why the ultra-violet absorption spectra of these two compounds are identical. The reactions most likely to occur during the Raney nickel treatment are either (*a*) a dehydrogenation, in which case A would presumably have structure (VI), which would be $C_{20}H_{14}ON_2$, as compared with $C_{20}H_{16}ON_2$ previously reported for ketoyobyrine, or (*b*) an isomerisation such as that encountered in the conversion of strychnine and brucine into their *neo*-isomerides by Chakravarti and Robinson (*J.*, 1947, 78), in which case A would be $C_{20}H_{16}ON_2$ and might be represented by structure (V) 6-*keto*-7 : 8-[1′ : 2′-(3′-*methylbenzo*)]-1 : 2-(2′ : 3′-*indolo*)-9 : 10-*dihydropyridocoline*. The analytical figures for $C_{20}H_{14}ON_2$ and $C_{20}H_{16}ON_2$ scarcely differ sufficiently to enable decisive conclusions to be drawn; but if (*a*) is correct, then it should be possible to obtain A from (IV) by the action of oxidising agents. So far, no success has been achieved in this direction (*e.g.*, with iodine and potassium acetate in alcohol, with chromium trioxide in glacial acetic acid, or with platinum and oxygen in acetic acid).

As to the ultra-violet absorption spectra, it appears that the curves obtained really refer to the structure (IV), isomerisation of A to (IV) occurring very rapidly under the influence of ultra-violet light. Thus, a dilute alcoholic solution of A or of ketoyobyrine was stable for weeks in the dark; but when it was allowed to stand even in diffused daylight, the yellow colour and blue-green fluorescence disappeared in a day or so and a blue fluorescence developed, and evaporation of the solution led to the recovery of a pale yellow crystalline material, apparently identical with (IV) (*e.g.*, its solution in concentrated sulphuric acid was yellow). On the basis of (*a*) above, the light reaction must involve a hydrogenation of A at the expense of the solvent alcohol; but it was found that this change occurs also in glacial acetic acid, which is not reducing in properties. Attempts to carry out a quantitative catalytic hydrogenation of ketoyobyrine were unsuccessful on account of its low solubility in acetic acid and alcohol; hydrogenation with platinum under pressure led to extensive hydrogenation, as shown by the high solubility of the product in organic solvents.

Thus assumption (*b*) above is supported. It may seem surprising that A and ketoyobyrine (both obtained under dehydrogenating conditions) should have structure (V) rather than (VI); but it must be borne in mind that the ring system of 4 (or 6)-ketopyridocoline (IX) does not constitute an aromatic system, and very little is known about its chemistry, although Clemo, Morgan, and Raper (*J.*, 1936, 1025) have described a yellow crystalline compound, whose solutions exhibit an intense green fluorescence, formulated as 4-keto-1-carbethoxy-3-(2′-pyridyl)-pyridocoline. To settle this matter finally, it is intended to investigate the ozonolysis of ketoyobyrine and related substances, and to attempt the synthesis of model compounds, including those having the ring-structure of (IX). It is noteworthy that recent work by Goutarel and Janot and Prelog (*Experientia*, 1948, **4**, 24) and by Prelog (*Helv. Chim. Acta*, 1948, **31**, 588) suggests that the alkaloid sempervirine has structure (VII) with CH_2 in place of CO.

Meanwhile, this slight doubt does not invalidate the implication of this work to the structure of yohimbine itself—namely, that it confirms the location of the carbomethoxy-group at C_{16}, and hence (indirectly) structure (I) for the alkaloid, since there is much evidence that the carbomethoxy- and the hydroxyl group are attached to adjacent carbon atoms.

While the above work was in progress, preliminary experiments on other possible routes to the synthesis of compounds of similar ring structure to the above were begun. These are briefly recorded below. (1) Attempts to condense tryptamine with *o*-nitrophenylpyruvic acid or *o*-nitrobenzaldehyde were unsuccessful. (2) By carrying out a Claisen condensation between *o*-tolunitrile and ethyl oxalate, o-*cyanophenylpyruvic acid* was obtained; but attempts to condense this with tryptamine were unsuccessful. (3) Ethyl ω-bromo-*o*-toluate was condensed with ethyl malonate, and the product hydrolysed to o-*carboxybenzylmalonic acid*. This is a possible intermediate for the synthesis of (X), from the phenylhydrazone of which (III) might be obtained by the Fischer indole synthesis.

Further work attempting to clarify still further the chemistry of yohimbine and related alkaloids is in progress.

Experimental.

1-(2 : 3-*Dimethylbenzoyl*)-β-*carboline* (II).—*o*-3-Xylidine, purified through its acetyl derivative (Cocker, *J.*, 1946, 38), was converted into 2 : 3-dimethylbenzoyl chloride (Brunner, Hofer, and Stein, *Sitzungsber. Akad. Wiss. Wien*, 1934, IIB, **142**, 302).

A mixture of β-carboline (Harvey, Miller, and Robson, *J.*, 1941, 158) (50 mg.) and 2 : 3-dimethylbenzoyl chloride (160 mg.) was heated for 2½ hours at 180°. After cooling, water and dilute sodium hydroxide solution were added; the resulting oil solidified after being stirred with the addition of a drop or two of ether. The *carboline* (II) was collected, washed with water, and recrystallised twice from methanol–water (charcoal) and twice from benzene–light petroleum (b. p. 60—80°), affording long, thin, colourless prisms, m. p. 151—153° (60 mg.) (Found: C, 79·9; H, 5·45. $C_{20}H_{16}ON_2$ requires C, 80·0; H, 5·35%). This was soluble in dilute hydrochloric acid, being reprecipitated by dilute sodium hydroxide solution.

N-(β-*Indolylethyl*)*homophthalamic Acid*.—A warm solution of tryptamine (1·15 g.) in pure, dry chloroform (25 c.c.) was added to one of homophthalic anhydride (1·15 g.) in chloroform (25 c.c.), and the mixture heated under reflux for 2 hours, during which the acid crystallised out in practically pure condition. After cooling, the product (2 g., m. p. 144°) was collected and washed with chloroform (Found: C, 70·4; H, 5·6. Calc. for $C_{19}H_{18}O_3N_2$: C, 70·8; H, 5·6%). Methylation in the way described by Schlittler and Allemann (*loc. cit.*) afforded the *methyl* ester as an oil which rapidly set to a solid, m. p. 99—101°; from benzene–light petroleum (b. p. 60—80°) this separated as colourless needles, m. p. 106°, after drying at 80°/1 mm. (Found: C, 71·8; H, 6·25. $C_{20}H_{20}O_3N_2$ requires C, 71·45; H, 5·95%).

6-*Keto*-7 : 8-*benzo*-1 : 2-(2′ : 3′-*indolo*)-3 : 4-*dihydropyridocoline* (VII).—The above crystalline methyl ester (0·7 g.) was cyclised as described by Schlittler and Allemann (*loc. cit.*) except that the reaction was carried out in an atmosphere of pure, dry nitrogen. After removal of phosphoryl chloride, the residue was treated with water, the resulting red solid collected, washed with water, dissolved in 95% ethanol (250 c.c.), and the solution boiled with charcoal, filtered, concentrated, and allowed to cool; the *compound* (VII) (0·31 g., m. p. 299°) which separated, recrystallised from ethanol, formed pale yellow needles, m. p. 299° (Found: C, 79·8; H, 4·9. $C_{19}H_{14}ON_2$ requires C, 79·7; H, 4·9%). Light absorption in ethanol: $\lambda_{max.}$ 3430, 3640 A., log ε 4·54, 4·52; $\lambda_{min.}$ 2890, 3560 A., log ε 3·75, 4·47.

6-*Keto*-7 : 8-*benzo*-1 : 2-(2′-3′-*indolo*)-9 : 10-*dihydropyridocoline*.—A solution of the above compound (32 mg.) in dry xylene (15 c.c.) was heated under reflux for 13 hours with a small amount of Raney nickel (washed first with absolute alcohol, then several times with xylene). The experiment was carried out in the absence of strong illumination. The hot solution was filtered, and on cooling, clusters of bright yellow needles separated. The *pyridocoline* (29 mg.) was filtered off, washed with benzene, and recrystallised from absolute alcohol, giving bright yellow crystals which were dried at 80°/1 mm.; m. p. *ca.* 295—310°, depending on rate of heating (Found: C, 79·9; H, 5·35. $C_{19}H_{14}ON_2$ requires C, 79·7; H, 4·9%).

Fission of (VII). This compound (0·15 g.) was refluxed for 11 hours with amyl alcohol (3 c.c.) and potassium hydroxide (0·15 g.) (bath temp., 180—185°). After cooling, the mass was extracted with water (20 c.c.), some undecomposed material (50 mg., m. p. 297°, decomp.) being recovered by filtration. The solution was extracted with ether, and the extract washed several times with dilute sodium hydroxide solution, then with dilute hydrochloric acid (extract A), the remaining ethereal amyl-alcoholic solution being referred to as solution B. The combined alkaline solution and washings were acidified (hydrochloric acid), extracted with ether (aqueous solution = C), the extract dried (Na_2SO_4), and the ether removed, leaving a brownish solid (40 mg., m. p. 97—100°). This was boiled in benzene solution with charcoal, filtered, the benzene removed, and the residue recrystallised from light petroleum (b. p. 60—80°), giving colourless needles, m. p. 103—104° (Found: C, 71·0; H, 6·1. Calc. for $C_9H_8O_2$: C, 70·6; H, 5·9%); mixed m. p. with *o*-toluic acid 103—105°.

Extract A (above) was basified (sodium hydroxide solution), extracted with ether, the extract dried (K_2CO_3), the ether removed, and the residue recrystallised twice from benzene–light petroleum (b. p. 60—80°), affording a small amount of colourless crystals, m. p. 197—198° (sintering at 191°) (mixed with β-carboline, prepared by method of Harvey, Miller, and Robson, *loc. cit.*, m. p. 197—198°, sintering at 191°), soluble in dilute hydrochloric acid to give a colourless solution with a blue fluorescence.

Solution B (above) was evaporated to dryness (water-bath/reduced pressure), giving a further 10 mg. of undecomposed material.

Solution C (above) was neutralised with sodium hydrogen carbonate, and extracted with ether; but the extract left no residue on evaporation.

β-o-*Tolylpropionic Acid*.—Technical *o*-xylene was brominated as described by Atkinson and Thorpe (*J.*, 1907, **91**, 1695), and the once-distilled monobromo-compound (b. p. 215—218°) used for the following preparation. Ethyl malonate (9·1 g.) was added to a warm solution of sodium (1·3 g.) in absolute alcohol (30 c.c.), ω-bromo-*o*-xylene (10 g.) was added during 20 minutes, and the mixture refluxed for a further 100 minutes. The bulk of the alcohol was removed by distillation, the residue cooled, treated with water, extracted with ether, the extract dried (Na_2SO_4), the ether removed, and the residue distilled, the fraction of b. p. 165—180°/11 mm. (6·3 g.) being collected. This was heated in an open flask for 3 hours on the water-bath with a solution of potassium hydroxide (5·5 g.) in water (5·5 c.c.), the water lost by evaporation being replaced from time to time. After cooling, the solution was acidified (hydrochloric acid), extracted with ether, the extract dried ($CaCl_2$), the ether removed, and the residue heated for 30 minutes at 160°, and then distilled, giving β-*o*-tolylpropionic acid (3·1 g.), b. p. 160—170°/12 mm., m. p. 91—102°, which was then recrystallised from alcohol–water.

Methyl N-(β-*Indolylethyl*)-6-*methylhomophthalamate*.—A solution of tryptamine (0·34 g.) in warm chloroform (8·5 c.c.) was added to one of 6-methylhomophthalic anhydride (0·37 g.) in chloroform (7·5 c.c.). The mixture was heated under reflux for 5 hours, cooled in ice, and extracted with cold dilute sodium hydroxide solution. The yellow extract was extracted with ether, and acidified (hydrochloric acid) in the cold. The precipitated oil was taken up in chloroform, the extract dried (Na_2SO_4), the solvent removed, and the resulting gum left overnight in a vacuum desiccator. It was then dissolved

in a little methanol, and the solution cooled in ice and treated with excess of an ethereal solution of diazomethane. After 30 minutes, the solution was evaporated to dryness (water-bath), and the residue kept in a vacuum desiccator. The resulting gum, on being stirred with a little ether, solidified. The product (0·5 g., m. p. 127—130°) was collected, washed with a little ether, dried in a vacuum desiccator, and the bulk used in the following cyclisation. A portion was recrystallised three times from benzene containing a little light petroleum (b. p. 60—80°) and afforded the *methyl* ester as large tablets, m. p. 139—140° (Found: C, 71·6; H, 6·05. $C_{21}H_{22}O_3N_2$ requires C, 72·0; H, 6·3%).

6-*Keto*-7 : 8-[1′ : 2′-(3′-*methylbenzo*)]-1 : 2-(2′ : 3′-*indolo*)-3 : 4-*dihydropyridocoline* (IV).—The above ester (0·44 g.) was refluxed with phosphoryl chloride (7 c.c.) for 50 minutes in an atmosphere of nitrogen, and the *product* (0·16 g.) isolated as in the preparation of (VII). It separated from alcohol as pale yellow plates or needles, m. p. *ca.* 320° (decomp.), depending on rate of heating (Found: C, 79·15; H, 5·55; C, 79·40; H, 4·95. $C_{20}H_{14}ON_2$ requires C, 80·0; H, 5·3%). Light absorption in ethanol: $\lambda_{max.}$ 3470, 3670, 3850 A., log ε 4·5, 4·5, 4·42; $\lambda_{min.}$ 2920, 3570, 3770 A., log ε 3·75, 4·42, 4·36.

6-*Keto*-7 : 8-[1′ : 2′-(3′-*methylbenzo*)]-1 : 2-(2′ : 3′-*indolo*)-9 : 10-*dihydropyridocoline* (V).—A solution of (IV) (30 mg.) in xylene (20 c.c.) was heated under reflux for 11 hours with Raney nickel. On cooling, the filtered solution deposited clusters of bright yellow needles (24 mg.). Recrystallisation of the *product* from absolute alcohol (charcoal) afforded bright yellow prisms, m. p. *ca.* 322° (decomp.), depending on rate of heating (Found: C, 78·8; H, 5·4. $C_{20}H_{16}ON_2$ requires C, 80·0; H, 5·3%).

o-*Cyanophenylpyruvic Acid.*—Potassium *tert.*-butoxide, from potassium (1 g.) and dry *tert.*-butanol (30 c.c.), was heated for 15 minutes at 150°/15 mm., and then cooled. Dry benzene (20 c.c.), ethyl oxalate (1·7 c.c.), and o-tolunitrile (1·5 c.c.) were added, the mixture heated for 2 hours on the water-bath, cooled, and water then added. The dark-red aqueous layer was separated, the benzene layer extracted with dilute sodium hydroxide solution, and the combined alkaline solutions extracted with ether, and acidified (hydrochloric acid) with cooling. The product was extracted with chloroform, the extract dried (Na_2SO_4), the solvent removed, the residue stirred with a little benzene, and the resulting solid collected, washed with benzene and dried, giving the *acid*, 0·45 g., m. p. 160° (decomp.). A solution of this in ethyl acetate was boiled with charcoal, filtered, and diluted with an equal volume of hot benzene. On cooling, clusters of pale yellow needles, m. p. 160° (decomp.), separated (Found: C, 63·7; H, 4·0. $C_{10}H_7O_3N$ requires C, 63·5; H, 3·7%).

Attempted Condensation of the Above Acid with Tryptamine.—Attempts to condense the pyruvic acid with tryptamine hydrochloride in aqueous or aqueous–alcoholic solutions led to recovery of tryptamine as the only basic product. When a solution of the acid (60 mg.) in alcohol (2 c.c.) was heated with one of tryptamine hydrochloride (70 mg.) in alcohol (3 c.c.) for 2 days on the water-bath, the bulk of the alcohol distilled off, dilute sodium hydroxide solution added to the residue, the mixture extracted with ether, and the extract kept overnight with a little dilute hydrochloric acid, a pale yellow solid separated. This was collected, washed with ether, and shaken with dilute sodium hydroxide solution and ether; the ethereal layer was dried (K_2CO_3), the ether removed, and the residue recrystallised from benzene–light petroleum (b. p. 60—80°). A very small amount of pale yellow crystals, m. p. 240—245°, was obtained. They were basic, and when added to concentrated sulphuric acid containing a trace of sodium nitrite, they slowly gave an olive-green colour.

Ethyl o-*Carbethoxybenzylmalonate.*—The solution obtained by adding ethyl malonate (7·2 c.c.) to a warm one of sodium (1·1 g.) in absolute alcohol (50 c.c.) was added gradually with shaking to a hot solution of ethyl ω-bromo-o-toluate (Davies and Perkin, *J.*, 1922, **121**, 2207) (11·8 g.) in alcohol (10 c.c.). After 30 minutes' heating on the water-bath, the bulk of the alcohol was distilled off, the residue treated with water (solution was alkaline), extracted with ether, the extract dried (Na_2SO_4), the ether removed, and the residue distilled, the fraction, b. p. 165—168°/1 mm. (7·35 g.), of the *ethyl* ester being collected (Found: C, 63·2; H, 6·7. $C_{17}H_{22}O_6$ requires C, 63·3; H, 6·8%).

o-*Carboxybenzylmalonic Acid.*—A solution of the above ester (0·48 g.) in 95% alcohol (1·8 c.c.) was heated under reflux for 2 hours on the water-bath with 40% aqueous potassium hydroxide (1·8 c.c.). After distilling off the bulk of the alcohol, the residue was dissolved in water, acidified (hydrochloric acid), extracted with ether, the extract dried (Na_2SO_4), the ether removed, and the residue rubbed with a little benzene, whereupon it crystallised. The solid (0·19 g.) was collected, dissolved in ethyl acetate, the solution boiled with charcoal, filtered, concentrated, and diluted with hot benzene. On cooling, the *acid* separated as colourless needles, m. p. *ca.* 180—190° (decomp.), depending on rate of heating (Found: C, 55·85; H, 4·4. $C_{11}H_{10}O_6$ requires C, 55·5; H, 4·2%).

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[*Received, May 29th,* 1948.]

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111. *The Primary Thermal Oxidation Product of Squalene.*

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The product formed in the early stages of the thermal oxidation of squalene has been examined and found to consist substantially of a diperoxide in which four atoms of oxygen are combined with one squalene molecule. Two oxygen atoms are contained in a hydroperoxide group and two form an intramolecular peroxide ring; two oxygen atoms (one from each group) are attached to adjacent carbon atoms. The probable structure of this compound is suggested after consideration of certain kinetic data on the oxidation of polyisoprenes and related mono-olefins.

THE reaction of olefins with molecular oxygen forms primary products the nature of which depends upon the structure of the olefin. Mono-olefins and 1 : 4-dienes form α-methylenic

hydroperoxides, whereas the products from conjugated dienes are preponderantly disubstituted cyclic or polymeric peroxides. No similar characterisation has been made of the oxidation products of a further important type of unsaturated grouping, the 1 : 5-dienes, despite their obvious bearing on the problem of the oxidative ageing of natural rubber. We now report an examination of the product formed in the early stages of the oxidation of a representative of this class of olefin, namely the hexaisoprene, squalene.

The choice of this olefin was dictated partly by a desire to minimise any abnormal effects arising from the proximity of double bonds to the ends of the molecule (a possible objection to the use of the di-isoprene, dihydromyrcene) and partly because kinetic evidence (Bolland and ten Have, *Trans. Faraday Soc.*, **1949**, **45**, 93) makes it clear that in the thermal oxidation of this olefin the chain length exceeds 100. The product would thus contain almost 99% of the total combined oxygen in the form of the products from the chain propagation reactions (*i.e.*, the primary product).

In view of the polymeric nature of the hydrocarbon, it is obvious that, even if the oxygen reacts uniquely with the unsaturated centres, the oxidation product itself, and any of its derivatives, must contain a sufficient variety of species to preclude their separate isolation and identification by normally used experimental techniques. The present work has therefore of necessity been limited to the application of analytical methods which give quantitative estimates of chemical groupings in the oxidation product and certain of its derivatives. Certain finer details of the molecular structure of oxidised squalene cannot be established by this approach; it is, however, possible to demonstrate that the primary oxidation product combines certain of the structural characteristics of products derived from conjugated and mono-olefins in a manner which might have been anticipated from the particular spacing of double bonds in 1 : 5-polyenes.

Chemical Examination of Oxidised Squalene.—Earlier work on the oxidation of polyisoprenes (Farmer and Sutton, *J.*, 1942, 139) suggested that, although the oxygen combined in the initial stages of the reaction was converted quantitatively into hydroperoxide groups, yet the yield of hydroperoxide diminished as oxidation progressed. These observations were accounted for in terms of an α-hydroperoxidic primary product which was so thermally unstable as to reduce appreciably the overall yield in which it was obtained. This view requires modification, since careful measurement has now shown that the nature of the oxidised squalene is unchanged over a substantial range of oxidation.

This point has been established by following three analytical characteristics over a series of oxidised squalene samples containing up to 3% of combined oxygen (0·4 mole per mole of squalene) : (*a*) peroxide content, (*b*) active-hydrogen content, and (*c*) average total oxygen content of the fraction of squalene which has been oxidised. Peroxide contents, measured iodometrically and with ferrous thiocyanate reagent, and active-hydrogen contents are presented in the figure. Throughout the introduction of the first 3% of oxygen, each molecule of oxygen incorporated in the squalene introduces 0·90 atom of peroxidic oxygen (reactive towards the above two analytical reagents) and 0·50 atom of active hydrogen. The obvious implication is that one hydroperoxidic group is present in each oxidised molecule. A simple form of chromatographic technique achieves quantitative separation of the oxidised material from the unoxidised squalene. Determination of the amount of unattacked olefin recoverable from a known weight of oxidised squalene of known oxygen content gives at once the average oxygen content of the oxidised squalene (cf. Bolland and Koch, *J.*, 1945, 445). In this way it was found that throughout the total oxygen content range of 0·58 to 2·98%, each molecule of oxidised *product* contained just over four atoms of oxygen :

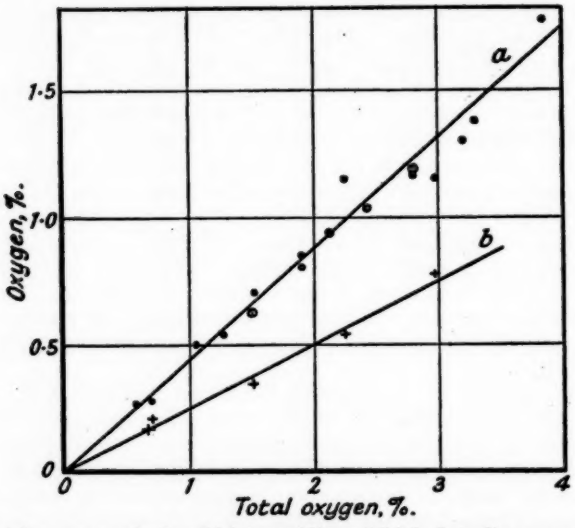
Total oxygen (%).	Atoms of oxygen/mole oxidised squalene : Found.	Calc.	Total oxygen (%).	Atoms of oxygen/mole oxidised squalene : Found.	Calc.
0·58	4·4	4·07	2·3	4·1	4·25
1·65	4·4	4·18	2·95	4·4	4·33
1·9	4·1	4·21	2·98	4·3	4·33

The calculated oxygen content of the oxidised squalene is derived on the suppositions that each time a squalene molecule is oxidised, four oxygen atoms are introduced, and that oxidation proceeds with equal facility at oxidised and unoxidised molecules.

Examination of the Separated Oxidation Product.—Analyses carried out on the oxidised fraction separated chromatographically agreed well with the indications obtained from analyses of the unfractionated oxidised samples as quoted above. The total oxygen content corresponded fairly well to the presence of four oxygen atoms per molecule, while peroxide and active

hydrogen analyses indicated the presence of two peroxidic oxygen atoms and one active hydrogen atom per molecule. Cryoscopic determinations of the molecular weight of the oxidised material gave a mean value of 490. Since the molecular weight of the squalene molecule oxidised to contain four oxygen atoms is 474, there is little evidence of intermolecular bridging by oxygen. Nevertheless, traces of gel were on occasion observed adhering to the reaction vessel at the end of experiments. This product which might well owe its insolubility to polymeric peroxidation was ignored in all the analyses quoted here.

Nature of Unreactive Oxygen.—Examination of the infra-red spectrum of oxidised squalene at the Department of Colloid Science, Cambridge, has revealed the presence of only trivial amounts of carbonyl oxygen. The two oxygen atoms per oxidised squalene molecule not reactive toward peroxide reagents do not therefore reside in ketonic, aldehydic, acidic, or ester groupings. Application of the method of Swern, Findley, Billen, and Scanlan (*Ind. Eng. Chem. Anal.*, **1947**, **19**, 414) for the estimation of epoxide oxygen revealed the presence of only a fractional amount of this grouping (0·06 epoxide group per oxidised molecule). The remaining possible groups—ether or cyclic peroxide—are sufficiently unreactive to analytical reagents to



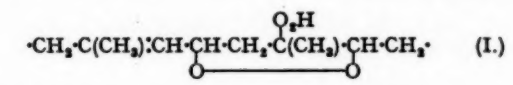
Relationship between total oxygen content and (a) *peroxidic and* (b) *hydroxylic oxygen contents in autoxidised squalene. Peroxide contents measured iodometrically and with ferrous thiocyanate reagent are indicated by* ⊙ *and* ● *respectively. The curves correspond to yields of* (a) 0·90 *atom of peroxidic oxygen and* (b) 0·50 *atom of hydroxylic oxygen per molecule of oxygen incorporated in the squalene.*

render their direct quantitative determination a difficult if not insoluble problem. Examination of the completely hydrogenated product does, however, provide a method with diagnostic possibilities.

Hydrogenation of Oxidised Squalene.—Samples of both oxidised squalene containing 2—3% of oxygen and the chromatographically separated oxidation product were completely hydrogenated in presence of Raney nickel. Measurements of total oxygen and active hydrogen contents and titrations with lead tetra-acetate were carried out on such hydrogenation products. The analytical results can be most satisfactorily interpreted if the overall effect of hydrogenation is to convert the hydroperoxide group in each oxidised molecule (thus accounting for the two peroxidic oxygen atoms and one active hydrogen atom per oxidised molecule shown to be present) into a hydroxyl group, with the simultaneous conversion of the two hitherto unaccounted-for oxygen atoms into two hydroxyl groups. The reactivity towards lead tetra-acetate requires further that two of these hydroxyl groups should be adjacent.

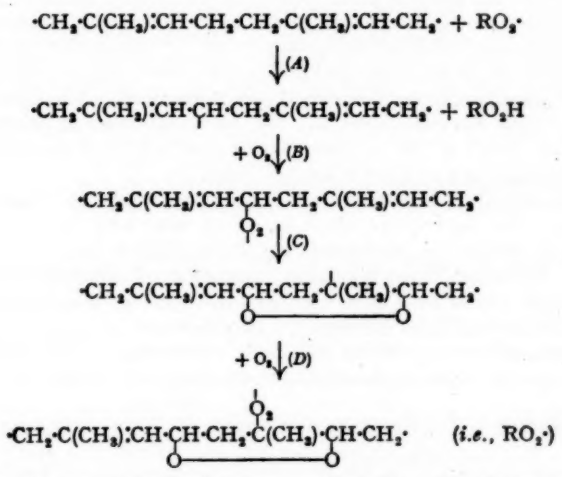
The only oxygenated groups which would fulfil these requirements are disubstituted peroxides of the cyclic or polymeric types: the former must predominate on the evidence of the molecular weight of the separated oxidation product (see above). Since four-membered ring peroxides may safely be ruled out, the inference from the lead tetra-acetate titrations is that in each oxidised squalene molecule the hydroperoxidic oxygen atoms and one oxygen atom in the cyclic peroxide are attached to two neighbouring carbon atoms.

Discussion.—It is not possible to formulate unequivocally the structure of the primary oxidation product from group analyses alone. It may be safely deduced, however, that the predominant oxidation product is a squalene molecule containing four oxygen atoms, two of which are contained in a hydroperoxide group and two in a cyclic peroxide group, with one atom from each grouping attached to adjacent carbon atoms. In advancing (I) as the probable



(I.)

structure, consideration has been given to kinetic evidence (*Trans. Faraday Soc., loc. cit.*) which provides a detailed knowledge of the mechanism by which squalene and oxygen interact. The cycle of reactions by which (I) would be formed during the propagation of the oxidation chain is as follows :



where RO_2H represents the completed oxidation product (I). The chain carrier $RO_2\cdot$ (like the other three types of radical concerned in the cycle) is reproduced after four reactions. This contrasts with the chain-propagation sequence in the case of many mono-olefins and 1 : 4-dienes where the cycle consists of only two reactions :

$$RH + RO_2\cdot \longrightarrow RO_2H + R\cdot \qquad R\cdot + O_2 \longrightarrow RO_2\cdot$$

where the chain carrier R· is derived from the olefin RH by removal of an α-methylene hydrogen and $RO_2\cdot$ by addition of an oxygen molecule to R· in an α-methylenic position and the main primary oxidation product is an α-methylenic hydroperoxide.

The critical point at which these two types of oxidation-chain cycle diverge lies in reaction (*C*) : in the case of squalene the peroxido-radical cyclises by interaction with the neighbouring double bond more efficiently than it abstracts a hydrogen atom from another squalene molecule. The nature of the elementary reaction ($RO_2\cdot$ + olefinic centre) undoubtedly determines the type of oxidation product which any olefin forms. Since, in general, the interaction of a peroxide radical with either a double bond or an α-methylene group appears to be of comparable efficiency, the balance in favour of one or the other mode of reaction may be altered by differences in the type of olefinic system. Thus the formation of α-methylenic hydroperoxides from mono-olefins and 1 : 4-dienes on the one hand and mainly polymeric peroxides from conjugated olefins on the other can be correlated with variations in the exothermicity of the reactions of the respective peroxide radicals with either the appropriate α-methylenic groups or double bonds (Bolland and Gee, *Trans. Faraday Soc.*, 1946, **42**, 244). In the present case the determining factor appears to be predominantly a steric one : the particular spacing of the double bonds must be sufficiently favourable for cyclisation of the peroxide radical to replace the normal hydrogen atom extraction process of peroxide radicals disposed next to a trisubstituted ethylenic bond—as exemplified by 1-methyl*cyclo*hexene (Farmer and Sundralingam, *J.*, 1942, 121). It is significant, however, that the chain propagation steps (*A*) and (*B*), in which the influence of the neighbouring double bonds should be small, may be shown to occur at almost precisely the same rates as the

corresponding reactions in the oxidation of a methyl-substituted mono-olefin like 4-methylhept-3-ene (Bolland and ten Have, *loc. cit.*).

Owing to the unsymmetrical nature of the unsaturated centres in squalene, the three propagation steps (*A*)—(*C*) may each be formulated in two ways, which differ only in the side of the double bond involved in the reactions. The alternatives given above were chosen as the more probable on the following grounds.

(*A*) The relative efficiencies of the analogous reaction $RO_2\cdot + RH \longrightarrow RO_2H + R\cdot$ for a series of olefins (Bolland, *Trans. Faraday Soc.*, in the press) lead to the conclusion that in the unsaturated system $\cdot\overset{1}{C}H_2\cdot C(CH_3){:}CH\cdot\overset{2}{C}H_2\cdot$ hydrogen abstraction from the α-methylene group (2) occurs some three times more readily than from α-methylene group (1).

(*B*) The attachment of the oxygen molecule in this reaction to the resonating hydrocarbon radical so that the double bond retains its original position is preferred on infra-red spectral evidence (obtained at Cambridge): oxidised squalene did not apparently contain the symmetrically disubstituted type of double bond which would necessarily result from oxygen addition at the tertiary carbon atom. It is, however, unlikely that differentiation between the two possibilities is clear-cut, since ample evidence of the insensitivity of this type of addition reaction to the structure of the hydrocarbon radical has been obtained (*idem, ibid.*).

(*C*) The accepted mechanisms of abnormal (peroxide initiated) addition to ethylenic bonds (Mayo and Walling, *Chem. Reviews*, 1940, **27**, 351) and formation of head-to-tail polymers (*e.g.*, Flory, *J. Polymer Sci.*, 1947, **2**, 36) require that radical addition should be more facile at the less highly substituted carbon atom in the double bond.

It is to be emphasised that the structure (I) represents only the most frequently occurring diperoxide structure: the alternative ways in which reactions (*A*) and (*B*) can proceed are sufficiently efficient to assure the presence of an appreciable proportion of other species in the oxidation product. Provided, however, that formation of six-membered peroxide rings by step (*C*) can proceed at either side of a trisubstituted double bond more efficiently than the competing intermolecular reactions involving a double bond or α-methylene group of another squalene molecule, the reaction product will be a diperoxide of the same type as (I). This situation arises with special force in the case of the central $\Delta^{1:5}$-system in the squalene molecule

$$\cdot\overset{1}{C}H_2\cdot C(CH_3){:}CH\cdot\overset{2}{C}H_2\cdot\overset{3}{C}H_2\cdot CH{:}C(CH_3)\cdot CH_2\cdot \qquad \cdot CH_2\cdot CH{:}CH\cdot\underset{O_2}{CH}\cdot$$
(II.) (III.)

(II). In reactions (*A*) and (*B*) the attachment of a peroxide radical group at carbon atom 2 or 3 will be favoured. Addition of this radical at the mono-substituted end of either of the neighbouring double bonds is unlikely, on the grounds that ring-closure of the radical (III) in the oxidation of mono-olefins (to give four- or five-membered rings) is not observed. The condition of diperoxide formation is thus again that addition of the peroxide radical at even the less favoured side of the neighbouring double bond should be more efficient than reaction with other olefin molecules.

Experimental.

Crude squalene obtained from basking shark liver oil was freed from saponifiable material and purified by repeated molecular distillation. Before use samples, in the form of a 2% solution in light petroleum (b. p. 40—60°), were passed through a 12-cm. alumina column.

Thermal oxidation of squalene was carried out in a constant-pressure apparatus of the type already described (Bolland, *Proc. Roy. Soc.*, 1946, *A*, **186**, 218; Bolland and ten Have, *Trans. Faraday Soc.*, 1947, **43**, 201). The temperature employed was 55° and the oxygen pressure *ca.* 760 mm. Hg.

Separation of Oxidised Product.—The oxidised material was quantitatively removed from known weights of oxidised squalene by passing the latter in the form of a 2% solution in light petroleum (b. p. 40—60°) through a 12-cm. alumina column. From the weight of squalene recovered from the solution, the oxygen content of the oxidised portion was calculated: elementary analyses on the recovered squalene demonstrated the absence of oxygenated groups (*e.g.*, C, 87·6$_5$; H, 12·3. Calc. for $C_{30}H_{50}$: C, 87·75; H, 12·25%). The oxidised *product* was eluted from the column with 150 ml. of acetone. Recovery yields averaged 90%. Evaporation of the acetone solution in a vacuum at room temperature left a slightly yellow liquid of viscosity similar to that of the original squalene. Analyses on different samples gave: (*a*) C, 76·7$_5$; H, 10·8; O (by diff.), 12·4$_5$; (*b*) C, 76·5$_5$; H, 10·6$_5$; O, 12·8; (*c*) C, 76·0; H, 10·6$_5$; O, 13·3$_5$; (*d*) C, 75·5; H, 10·6; O, 13·9%. The molecular weight, determined cryoscopically in benzene, was (*a*) 454, (*b*) 533 ($C_{30}H_{50}O_4$ requires C, 75·9; H, 10·62; O, 13·48%; *M*, 474). The peroxidic oxygen contents of three separated oxidised products measured colorimetrically were 5·75, 6·5, and 5·1%, showing that no marked decomposition had taken place during the chromatographic treatment.

Peroxide Determination.—Two distinct methods were used: (*a*) Dastur and Lea's iodometric procedure (*Analyst*, 1941, **66**, 90) and (*b*) the oxidation of ferrous to ferric thiocyanate, measured colorimetrically. In the latter case the effect of varying the concentration of the various constituents

of the reagent was studied systematically. It was found that the total acid concentration could be varied between 0·1N and 1·1N with no appreciable change in estimated peroxide content, but below certain critical concentrations the apparent peroxide content decreased with decreasing ferrous salt concentration, but increased with decreasing thiocyanate concentration. Increase in concentration of these three reagent constituents above these critical values had no appreciable effect on the colour developed. The reagent finally adopted varied slightly from that of Bolland *et al.* (*Trans. India Rubber Inst.*, 1941, **17**, 29) and consisted of 0·5 g. of ammonium thiocyanate in 100 ml. of 94% methanol/water, 0·5 ml. of 36N-sulphuric acid, and 0·04 g. of ferrous ammonium sulphate (dissolved in *ca.* 0·3 ml. water to ensure complete solubility when mixed with the methanol-rich reagent). The methanol was redistilled over ferric alum before use to remove oxidisable impurities. The reagent was used immediately after being made up.

Active-hydrogen Determinations.—These were carried out by the modified Zerewitinoff method described by Bolland (*ibid.*, 1941, **16**, 267).

Hydrogenations.—These were carried out in the conventional constant-pressure type of apparatus of 200-ml. capacity. Weighed samples were dissolved in 15—20 ml. of redistilled ethanol, and *ca.* 3 g. of Raney nickel added. Hydrogenation was usually complete in 7—10 hours. The catalyst was separated off by filtration through a wad of " Hyflo Super-cel " which was then washed with either petrol or ethanol, depending on whether unoxidised squalene was present in the hydrogenated sample or not. The filtrate, which was shown to be entirely free from hydroperoxide, was made up to known volume. Aliquots were pipetted into the active-hydrogen apparatus, and the solvent evaporated off in a vacuum at room temperature. The remainder was evaporated down and weighed. Losses during the above procedure were thus shown to be less than 2%. The reduced material was dissolved in 46% or 90% methanol–benzene mixture, depending on whether the starting material contained considerable amounts of squalene or not, before treatment with lead tetra-acetate.

Reaction with Lead Tetra-acetate.—This process was carried out according to Criegee's method (*Ber.*, 1931, **64**, 260). Aliquots of the reduced product were left for various periods in contact with 0·1N-lead tetra-acetate in anhydrous acetic acid. Maximum reaction was reached after about 6 hours. Compared with the reduced oxidation product, reduced squalene showed only slight reactivity toward lead tetra-acetate.

The following results were obtained with hydrogenated samples of separated and unseparated oxidation products. In each case the total number of hydroxyl groups and the number contained in 1 : 2-diol groupings per oxidised squalene molecule are calculated.

Total oxygen (%).	Active H (%).	No. of OH groups per oxidised mol.: Total.	As 1 : 2-diol.
	(*a*) Unseparated oxidised squalene.		
2·93	0·113	2·66	1·5
2·98	0·113	2·62	$1·5_5$
	(*b*) Separated oxidation product.		
—	0·491	2·31	1·5
—	0·428, 0·433	2·03	$1·5_5$
—	0·407, 0·412	1·93	—
—	—	—	1·6

These active-hydrogen values (*b*) should be regarded as minimum values: condensation between hydroxyl groups during the necessary drying treatment of the sample before active-hydrogen determination must inevitably be favoured by the relatively high hydroxyl content of the reduced separated oxidation product.

The total oxygen content of two samples of separated oxidation product after reduction averaged $10·4_5$% [C, 76·0; H, 13·6; O (by diff.), 10·4; and C, $76·3_5$, 76·4; H, 13·1, 13·1; O (by diff.), 10·5%].

The hydrogenation product of (I) would be $C_{30}H_{61}O_3$ (oxygen content, 10·2%) and would contain three hydroxyl groups (Found, *ca.* 2·6) and one 1 : 2-diol group (Found, 0·78).

This paper forms part of the programme of fundamental research undertaken by the Board of the British Rubber Producers' Research Association. The authors are indebted to Dr. G. Gee for advice and criticism during the progress of the work, to Dr. G. B. B. M. Sutherland for the infra-red examination of oxidised squalene samples, and to Dr. W. T. Chambers for carrying out the elementary analyses.

BRITISH RUBBER PRODUCERS' RESEARCH ASSOCIATION,
TEWIN ROAD, WELWYN, HERTS.

[*Received, June 5th*, 1948.]

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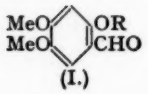
112. *The Chemistry of Fungi. Part I. The Synthesis of 6-Hydroxy-3 : 4-dimethoxyphthalic Acid.*

By J. B. D. MACKENZIE and ALEXANDER ROBERTSON.

The phthalic acid (VI, R = Et) has been synthesised from the aldehyde (I, R = H) by way of (I, R = Et), (II), (III), (IV), and (V), and shown to be identical with a specimen obtained by the degradation of the methyl ester of *O*-dimethylcitromycetin by comparison of the respective anhydrides. Similarly, the isomeric acid (VIII, R = Et) has been prepared from the aldehyde (VII).

By alkaline fission of the methyl ester of *O*-dimethylcitromycetin, Hetherington and Raistrick (*Phil. Trans.*, 1931, *B*, **220**, 209) obtained a phthalic acid derivative which they considered to be 6-hydroxy-3 : 4-dimethoxyphthalic acid (VI, R = H).* On account of the strong ferric reaction exhibited by this degradation product it seemed reasonably certain that the substance contained a hydroxyl group in the *o*-position to a carboxyl group, but, on the basis of the available evidence, the alternative structure (VIII, R = H) appeared to be equally feasible. In the course of studies on the structure of citromycetin and its derivatives it became clear that the orientation of this hydroxydimethoxyphthalic acid was an essential preliminary step, and accordingly the synthesis of the isomeric dimethoxyethoxyphthalic acids (VI, R = Et) and (VIII, R = Et) was undertaken.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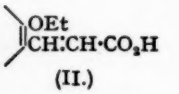
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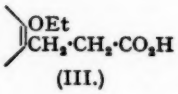
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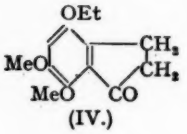
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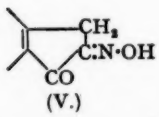
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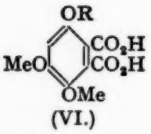
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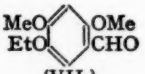
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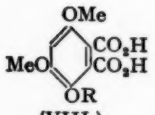

(VIII.)

Prepared from (I, R = H) by way of (I, R = Et) and (II), the β-*phenylpropionic acid* (III) was converted into the *indanone* (IV) in moderate yields by the action of aluminium chloride on the acid chloride from (III); cyclisation of (III) by means of phosphoric oxide in warm benzene gave only minute yields of (IV). The *oximino*-derivative (V) was prepared from (IV), and on oxidation with alkaline potassium permanganate gave rise to the phthalic acid (VI, R = Et), characterised by the formation of its anhydride. Comparison of the acid and its anhydride with the respective natural specimens prepared from citromycetin (*loc. cit.*) showed that they were identical, thus establishing that the hydroxydimethoxyphthalic acid from the methyl ester of *O*-dimethylcitromycetin has the orientation (VI, R = H). By the same series of reactions the isomeric 4 : 6-dimethoxy-3-ethoxyphthalic acid (VIII, R = Et) was prepared from the aldehyde (VII) and characterised by conversion into its *anhydride*.

Experimental.

4 : 5-*Dimethoxy-2-ethoxybenzaldehyde* (I, R = Et) (With L. M. Tunnicliffe).—2-Hydroxy-4 : 5-dimethoxybenzaldehyde, m. p. 107° (compare Head and Robertson, *J.*, 1930, 2434, who give m. p. 105°) (10 g.), was ethylated with ethyl iodide (5 ml.) and potassium carbonate (25 g.) in boiling acetone (300 ml.) in the course of 2 hours, and on isolation the *ethyl* ether separated from aqueous alcohol in colourless needles (10·5 g.), m. p. 105°, soluble in acetone, benzene, or chloroform (Found : C, 62·6; H, 6·9. $C_{11}H_{14}O_4$ requires C, 62·9; H, 6·7%). The 2 : 4-*dinitrophenylhydrazone* formed crimson needles, m. p. 252°, from chloroform (Found : N, 14·5. $C_{17}H_{18}O_7N_4$ requires N, 14·4%).

This aldehyde (2 g.) in acetone (50 ml.) at 50° was oxidised by gradual addition of a solution of potassium permanganate (3·2 g.) in water (70 ml.) in the course of 45 minutes, and ½ hour later the cooled mixture was cleared with sulphur dioxide and filtered. The resulting 4 : 5-*dimethoxy-2-ethoxybenzoic acid*, which separated when the greater part of the acetone was evaporated, was freed from traces of unchanged aldehyde by means of aqueous sodium hydrogen carbonate, and crystallised from ethyl acetate, forming flat parallelograms (1·8 g.), m. p. 149° (Found : C, 58·2; H, 6·3. $C_{11}H_{14}O_5$ requires C, 58·4; H, 6·2%). Prepared with diazoethane, the *ethyl* ester of this acid separated from light petroleum (b. p. 60—80°) in rectangular prisms, m. p. 63° (Found : C, 61·4; H, 6·9. $C_{13}H_{18}O_5$ requires C, 61·4; H, 7·1%).

Attempts to prepare the corresponding phthalide by condensation of 4 : 5-dimethoxy-2-ethoxybenzoic acid (1 g.) or its ester with chloral (0·75 g.) in concentrated sulphuric acid (2 ml.) at room temperature for 3 days, with or without subsequent heating to 80° for ½ hour, were unsuccessful. The only product isolated was the unchanged benzoic acid.

β-4 : 5-*Dimethoxy-2-ethoxyphenylpropionic Acid* (III).—A mixture of 4 : 5-dimethoxy-2-ethoxybenzaldehyde (5 g.), malonic acid (10 g.), pyridine (25 ml.), and piperidine (0·5 g.) was heated on the steam-bath for 4 hours and then at 120° for 30 minutes. The cooled mixture was treated with dilute hydrochloric acid (500 ml.), and the 4 : 5-*dimethoxy-2-ethoxycinnamic acid* (II) thus precipitated was collected and purified by crystallisation from aqueous alcohol, benzene, or light petroleum (b. p. 60—80°), forming pale yellow prisms (6·0 g.), m. p. 171°, soluble in chloroform, methanol, or ethyl acetate (Found : C, 61·8; H, 6·5. $C_{13}H_{16}O_5$ requires C, 61·9; H, 6·4%).

* Hetherington and Raistrick (*loc. cit.*) use, for 3 : 4 : 6-trihydroxyphthalic acid, the numbering 3 : 5 : 6-. On this system the compound (VI, R = H) would be 3-hydroxy-5 : 6-dimethoxyphthalic acid.—Editor.

The cinnamic acid (1 g.), dissolved in acetic acid (100 ml.), was hydrogenated with hydrogen and a palladium–charcoal catalyst, and on isolation the resulting *propionic acid* (III) separated from light petroleum (b. p. 60—80°) in colourless rhombic prisms (0·9 g.), m. p. 80°, soluble in alcohol or ethyl acetate (Found: C, 61·4; H, 7·4. $C_{12}H_{16}O_5$ requires C, 61·4; H, 7·1%).

6 : 7-*Dimethoxy*-4-*ethoxyindan*-1-*one* (With G. H. Jones).—The foregoing β-phenylpropionic acid (1 g.), dissolved in chloroform (50 ml.), was treated with phosphorus pentachloride (0·85 g.) and the mixture kept at room temperature for 2 hours. After removal of the solvent and phosphorus oxychloride under reduced pressure, more chloroform was added to the residue and the solution again evaporated. Freshly sublimed aluminium chloride (1 g.) was added to a solution of the residual acid chloride in benzene (75 ml.), and the mixture agitated for ½ hour, then maintained at 80° for 20 minutes, cooled, and poured on ice (500 g.). After addition of concentrated hydrochloric acid (20 ml.) to this mixture, the benzene layer was isolated, the aqueous liquor extracted with ether (6 × 100 ml.), and the combined benzene and ether solutions washed with aqueous sodium hydrogen carbonate, then with aqueous sodium hydroxide, and finally with water. Distillation of the residue left on evaporation of the dried extracts gave the *indanone*, b. p. 125°/0·005 mm., which formed colourless needles (0·3 g.), m. p. 117°, from light petroleum (b. p. 60—80°), soluble in alcohol, benzene, or ethyl acetate (Found: C, 65·8; H, 7·0. $C_{13}H_{16}O_4$ requires C, 66·1; H, 6·8%). The 2 : 4-*dinitrophenylhydrazone* separated from ethyl acetate in brick-red needles, m. p. 275° (decomp.) (Found: C, 54·5; H, 4·9; N, 13·4. $C_{19}H_{20}O_7N_4$ requires C, 54·8; H, 4·8; N, 13·5%).

3 : 4-*Dimethoxy*-6-*ethoxyphthalic Anhydride*.—A solution of the foregoing indanone (0·12 g.) and *iso*amyl nitrite (0·15 ml.) in methanol (0·5 ml.) was treated with concentrated hydrochloric acid (0·1 ml.) and then kept at 50° for ½ hour. The *oximino*-derivative, which separated from the cooled solution, was collected and recrystallised from methanol, forming pale yellow needles (0·08 g.), m. p. 221° (Found: N, 5·4. $C_{13}H_{15}O_5N$ requires N, 5·3%).

Cold saturated aqueous potassium permanganate was added dropwise to a solution of the foregoing oximino-compound (0·2 g.) in cold 5% aqueous potassium hydroxide (15 ml.) until the colour of the permanganate was no longer discharged. Sufficient sulphur dioxide was then slowly led into this mixture, kept at 0°, to clear the solution which was then acidified with hydrochloric acid, saturated with ammonium sulphate, and extracted with ether (30 ml. × 10). Evaporation of the combined dried extracts followed by crystallisation of the residue from ethyl acetate–light petroleum (b. p. 60—80°) gave 3 : 4-dimethoxy-6-ethoxyphthalic acid in colourless, slender prisms (0·1 g.), m. p. 195° (efferv.), freely soluble in ether, benzene, or ethyl acetate, and identical with a specimen prepared from citromycetin (*loc. cit.*) (Found: C, 53·4; H, 5·3. Calc. for $C_{12}H_{14}O_7$: C, 53·3; H, 5·2%). On being kept at 190°/14 mm. for 1 hour the acid decomposed, and the resulting anhydride formed a pale yellow sublimate. Recrystallised from ethyl acetate–light petroleum (b. p. 80—100°), this substance was obtained in colourless needles (0·05 g.), m. p. 196°, soluble in alcohol, ethyl acetate, or benzene, and was identical with a specimen prepared from a sample of the acid obtained from citromycetin (Found: C, 57·1; H, 4·8. Calc. for $C_{12}H_{12}O_6$: C, 57·1; H, 4·8%).

β-2 : 4-*Dimethoxy*-5-*ethoxyphenylpropionic Acid*.—Interaction of 2 : 4-dimethoxy-5-ethoxybenzaldehyde (Head and Robertson, *loc. cit.*) (7·5 g.), malonic acid (20 g.), pyridine (35 ml.), and piperidine (0·5 ml.) at about 95° for 4 hours and then at 120° (oil-bath) for ½ hour gave rise to 2 : 4-*dimethoxy*-5-*ethoxycinnamic acid* which separated from dilute alcohol in lemon needles (7 g.), m. p. 134°, freely soluble in alcohol or benzene (Found: C, 62·0; H, 6·5. $C_{13}H_{16}O_5$ requires C, 61·9; H, 6·4%). Hydrogenation of this acid (2·5 g.) with aid of a palladium–charcoal catalyst furnished the *propionic acid* which formed colourless elongated prisms (2 g.), m. p. 106°, from light petroleum (b. p. 60—80°), soluble in the common organic solvents except light petroleum (Found: C, 61·2; H, 7·2. $C_{13}H_{18}O_5$ requires C, 61·4; H, 7·1%).

4 : 6-*Dimethoxy*-7-*ethoxyindan*-1-*one*.—The foregoing β-phenylpropionic acid was converted into the acid chloride by the way used for the isomeride (III). A solution of the acid chloride (from 2·5 g. of acid) in benzene (100 ml.) was added dropwise to a mechanically-stirred mixture of benzene (100 ml.) and freshly sublimed aluminium chloride (2·1 g.) at 40°. The mixture was warmed to 70° in the course of 15 minutes, then kept there for the same period, and poured on ice (200 g.) and dilute 2N-hydrochloric acid (100 ml.). After isolation by the method employed for the isomeride (IV), the *indanone* was purified by distillation in a vacuum, b. p. 125—130°/0·005 mm., and then by crystallisation from light petroleum (b. p. 60—80°), forming colourless needles (1 g.), m. p. 105°, soluble in the common organic solvents except light petroleum (Found: C, 65·8; H, 6·6. $C_{13}H_{16}O_4$ requires C, 66·1; H, 6·8%). The 2 : 4-*dinitrophenylhydrazone* separated from ethyl acetate in brick-red needles, m. p. 264° (decomp.) (Found: N, 13·4. $C_{19}H_{20}O_7N_4$ requires N, 13·5%).

This indanone (1 g.) was nitrosated by the procedure adopted for (IV), and on isolation the *oximino*-derivative formed yellow needles (0·7 g.), m. p. 195—196° (decomp.), from ethyl acetate–light petroleum (b. p. 80—100°) (Found: N, 5·7. $C_{13}H_{15}O_5N$ requires N, 5·3%).

4 : 6-*Dimethoxy*-3-*ethoxyphthalic Anhydride*.—Saturated aqueous potassium permanganate was added dropwise to a solution of the foregoing oximino-compound (0·5 g.) in 5% aqueous potassium hydroxide (20 ml.) until a permanent pink colour remained, and the solution then cleared with sulphur dioxide and acidified. After isolation by means of ether, the phthalic acid was converted into the *anhydride* by being heated in a vacuum at 180°/0·05 mm. This derivative was obtained as a pale yellow sublimate, and on crystallisation from ethyl acetate–light petroleum (b. p. 60—80°) formed colourless elongated parallelograms (0·1 g.), m. p. 149°, soluble in the usual organic solvents except light petroleum (Found: C, 57·4; H, 5·0. $C_{12}H_{12}O_6$ requires C, 57·1; H, 4·8%).

The authors are indebted to Messrs. Imperial Chemical Industries Limited for a research grant.

University of Liverpool. [*Received, March 11th*, 1948.]

113. *Analgesics. Part I. Esters and Ketones derived from α-Amino-ω-cyano-ωω-diarylalkanes.*

By D. J. Dupré, J. Elks, B. A. Hems, (Miss) K. N. Speyer, and (in part) R. M. Evans.

A number of basic cyanides (V) have been prepared either (*a*) by reaction of a diarylmethyl cyanide with a chloro-amine $R_2N\cdot[CH_2]_n\cdot Cl$, or (*b*) by treatment of a diarylmethyl cyanide with an *αω*-dihalogeno-paraffin, and reaction of the resulting halogeno-cyanide with a secondary amine. The amino-cyanides were converted into amino-ketones by treatment with Grignard reagents, and into amino-esters by direct esterification with alcoholic sulphuric acid.

The acids $R_2N\cdot CH_2\cdot CH_2\cdot CPh_2\cdot CO_2H$ (R = Me or Et) on treatment with thionyl chloride gave the 3 : 3-diphenyl-1-alkylpyrrolid-2-one; the homologous acid, $Et_2N\cdot CH_2\cdot CH_2\cdot CH_2\cdot CPh_2\cdot CO_2H$, on similar treatment, gave an acid chloride which showed no tendency to cyclise.

The analgesic activities of the amino-esters and amino-ketones are given.

Although morphine has been widely used as an analgesic for a very long time, it is known to have many disadvantages; in particular, its depressant effect on the respiratory centre and its pronounced tendency to cause addiction are serious drawbacks in clinical practice. Much work has been done, particularly in America, on the preparation of derivatives of morphine that might retain analgesic activity while lacking the undesirable effects of the parent compound (Small, Eddy, Mosettig, and Himmelsbach, Public Health Service, Supplement No. 138, U.S. Treasury Dept., Washington, 1938), and some success has now been achieved with the introduction of methyldihydromorphinone (metopon) (Lee, *J. Pharm. Exp. Ther.*, 1942, **75**, 161). Many attempts have also been made by these and other workers to prepare a synthetic substitute for morphine; the first useful compound to emerge from this work was pethidine, the hydrochloride of ethyl 4-phenyl-1-methylpiperidine-4-carboxylate (Eisleb, *Ber.*, 1941, **74**, 1433) which has about one-third of the analgesic activity of morphine, and has been widely used in the past few years. Although a great many compounds related to pethidine have been prepared and tested (Eisleb, *loc. cit.*; Schaumann, *Arch. exp. Path. Pharm.*, 1940, **196**, 109; Bergel *et al.*, *J.*, 1944, 261, 265, 267, 269; MacDonald, Woolfe, Bergel, Morrison, and Rinderknecht, *Brit. J. Pharmacol.*, 1946, **1**, 4), only one appears to be of any importance, namely, ethyl 3-phenyl-1-methylpiperidine-3-carboxylate (β-pethidine), which has been tested clinically (Glazebrook and Branwood, *Lancet*, 1945, ii, 528).

A new class of compounds with analgesic activity was described by Bockmühl and Ehrhart (U.S.P. 2,230,774); these are of the type represented by formula (I; R = H or alkyl,

(I.) $Alk_2N\cdot CHR\cdot CH_2\cdot CPh_2\cdot COR'$ $\qquad$ $R_2N\cdot[CH_2]_n\cdot CAr_2\cdot COR'$ (II.)

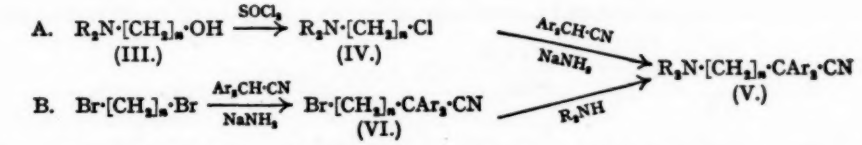
R′ = alkoxyl). Considerably more information about these compounds was obtained from Germany at the end of the war, the most complete report being that of Kleiderer, Rice, Conquest, and Williams (Report No. 981, Office of the Publication Board, Department of Commerce, Washington, D.C.). In general, ketones of type I (R = H or alkyl, R′ = alkyl) were more effective than the corresponding esters, and the compounds that appeared to be most favoured were 6-dimethylamino-4 : 4-diphenylhexan-3-one (I; Alk = Me, R = H, R′ = Et) and 6-dimethylamino-4 : 4-diphenylheptan-3-one (I; Alk = Me, R = Me, R′ = Et), the latter being known as amidone. Amidone was said to have 5—10 times the activity of pethidine, and it has recently been investigated pharmacologically and clinically both in this country and in America (Scott and Chen, *J. Pharm. Exp. Ther.*, 1946, **87**, 63; *Science*, 1946, **104**, 587; Hewer and Keele, *Lancet*, 1947, ii, 281; Steel and Gunderson, *ibid.*, 1947, ii, 370; Isbell *et al.*, *J. Amer. Med. Assoc.*, 1947, **135**, 888).

We have prepared a number of compounds of the same general type, with a view to determining the effect on the analgesic activity of alterations in various parts of the molecule. We did not have access to the full report of the German work until the investigation was well advanced, and some duplication has resulted.

In this paper we describe the preparation of a number of esters (II; R′ = OEt) and ketones (II; R′ = alkyl or Ph) with terminal basic substituents. The synthesis of amidone and its analogues is dealt with in the following paper.

Both esters and ketones were prepared, as described below, from the appropriate cyanides

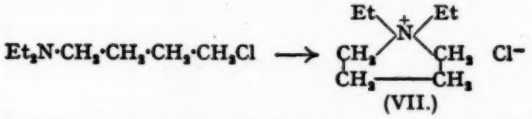
(V). Two methods were employed for the synthesis of unbranched cyanides with terminal basic substituents :



Method A.—The amino-alcohols (III; $n = 2$, 3, and 4) were, in most instances, prepared by standard methods. 2-Pyrrolidinoethanol was obtained by the reaction of 1 : 4-dibromobutane with ethanolamine in alcohol (cf. v. Braun, *Ber.*, 1911, **44**, 1252). 2-(2 : 6-*Dimethylmorpholino*)-*ethanol* was prepared similarly from di-(2-chloro*iso*propyl) ether and ethanolamine in the presence of potassium carbonate. The chloro-ether and the derivatives of 2 : 6-dimethylmorpholine prepared from it can exist in *meso*- and (±)-forms; the solid derivatives prepared in this series melted over ranges of several degrees, and were probably mixtures of the two forms.

The amino-alcohols were converted into the chloro-amine hydrochlorides by treatment with thionyl chloride in benzene (cf. Slotta and Behnisch, *Ber.*, 1935, **68**, 754) or in chloroform. The free bases (IV) were liberated from their hydrochlorides immediately before use.

Reaction of the chloro-amines (IV; $n = 2$ or 3) with diarylmethyl cyanides in the presence of sodamide in benzene (Bockmühl and Ehrhart, *loc. cit.*) gave satisfactory yields of the cyanides (V; $n = 2$ or 3). All attempts to prepare 5-diethylamino-1 : 1-diphenylamyl cyanide (V; R = Et, Ar = Ph, $n = 4$) by reaction of 1-chloro-4-diethylaminobutane with sodiodiphenylmethyl cyanide were unsuccessful; this failure is presumably due to the ready cyclisation of the free chloro-amine to *NN*-diethylpyrrolidinium chloride (VII), which was rapidly deposited from a cold ethereal solution of the base, and was characterised as the *picrate*. Even by working rapidly the cyclisation could not be prevented, and the use of method A for the preparation of this type of compound had to be abandoned.



(VII.)

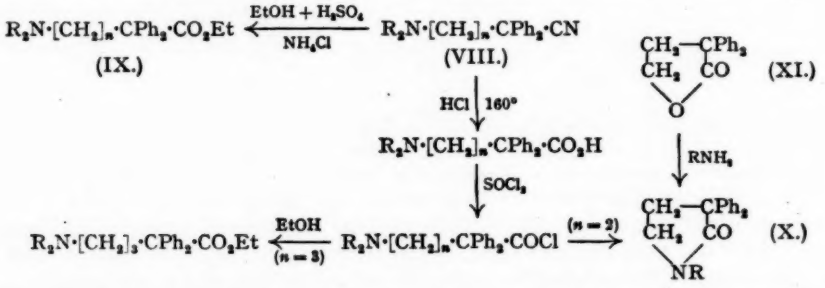
Method B.—The sodium derivative of diphenylmethyl cyanide, prepared by means of sodamide in boiling benzene, reacts readily with excess of ethylene dichloride or ethylene dibromide to give the 3-halogeno-1 : 1-diphenylpropyl cyanide accompanied by only a small quantity of 1 : 4-*dicyano*-1 : 1 : 4 : 4-*tetraphenylbutane* (cf. Murray and Cloke, *J. Amer. Chem. Soc.*, 1946, **68**, 126). 3-*Bromo*-1-*phenyl*-1-p-*tolylpropyl cyanide* was prepared similarly from phenyl-*p*-tolylmethyl cyanide and ethylene dibromide. In the same way, 1 : 3-dibromopropane and 1 : 4-dibromobutane react with sodiodiphenylmethyl cyanide to give the compounds (VI; Ar = Ph, $n = 3$) and (VI; Ar = Ph, $n = 4$), respectively; the latter compound could not be obtained pure, but the crude product, separated as far as possible from 1 : 6-*dicyano*-1 : 1 : 6 : 6-*tetraphenylhexane*, was used for the next stage.

Several attempts to cause ethylene dibromide to react with diphenylmethyl cyanide in the presence of sodium ethoxide in alcohol or benzene were unsuccessful (cf. B.P. 563,665).

Attempts to cause 3-chloro-1 : 1-diphenylpropyl cyanide to react with piperidine in benzene, toluene, or aqueous alcohol containing sodium hydrogen carbonate gave only traces of the required 1 : 1-*diphenyl*-3-*piperidinopropyl cyanide* (V; $R_2 = -[CH_2]_5-$, Ar = Ph, $n = 2$). The bromo-compounds (VI; $n = 2$), however, reacted readily with a number of secondary amines. The reaction conditions varied from one amine to another but generally the reaction was carried out without a solvent or in xylene, excess of base being used to neutralise the liberated hydrogen bromide. The cyanides (V; $n = 2$) were usually obtained in satisfactory yield. The *compounds* (VI; Ar = Ph, $n = 3$) and (VI; Ar = Ph, $n = 4$) both reacted readily with morpholine to give the *cyanides* (V; $R_2 = -CH_2·CH_2·O·CH_2·CH_2-$, Ar = Ph, $n = 3$) and (V; $R_2 = -CH_2·CH_2·O·CH_2·CH_2-$, Ar = Ph; $n = 4$).

The conversion of the cyanides (VIII) into the corresponding ethyl esters (IX) was achieved by Bockmühl and Ehrhart (*loc. cit.*) by preliminary sulphuric acid hydrolysis to the carboxylic acid, followed by esterification in the presence of sulphuric acid, water being removed as a water–alcohol azeotrope. This method proved to be unsatisfactory in our hands, but a direct

conversion into the ester was carried out by heating the cyanide with alcohol, concentrated sulphuric acid, and ammonium chloride in a sealed tube at 160° (cf. Bergel, Morrison, and Rinderknecht, *J.*, 1944, 265). While this method gave fair yields of the substituted butyric esters (IX; $n = 2$), the substituted *valeric ester* (IX; R = Et, $n = 3$) could not be obtained



pure when prepared thus. This compound was, however, prepared successfully by hydrolysis of 4-diethylamino-1 : 1-diphenylbutyl cyanide (VIII; R = Et, $n = 3$) with hydrochloric acid at 160°, conversion of the *carboxylic acid* into the acid chloride by means of thionyl chloride, and treatment of the acid chloride with alcohol.

TABLE I.

Analgesic Activities of Amino-ketones and Amino-esters.

Compound. R·CH₂·CH₂·CPh₂·COR′		Analgesic activity (pethidine = 1).
R =	R′ =	
Me_2N	OEt	¾—1
Et_2N	OEt	0—¼ (*a*)
Piperidino	OEt	1 (*a*, *c*)
Morpholino	OEt	1 (*a*)
Me_2N	Me	0—⅓ (*a*)
Me_2N	Et	1 (*a*, *d*)
Me_2N	Pr^n	⅔ (*a*)
Me_2N	Ph	0 (*a*)
Et_2N	Et	¾—1
Pr^n_2N	Et	0—⅓
Bu^n_2N	Et	0—⅓
$(PhCH_2)NMe$	Et	0
$(PhCH_2)_2N$	Et	(*e*)
Pyrrolidino	Et	4 (*f*)
Piperidino	Et	2—3 (*a*, *b*, *f*)
2-Methylpiperidino	Et	0
3-Methylpiperidino	Et	0—⅓
4-Methylpiperidino	Et	3 (*f*)
2 : 6-Dimethylpiperidino	Et	0—⅓
Morpholino	Me	½—1
Morpholino	Et	⅐ (*a*, *d*, *f*)
Morpholino	Pr^n	1
2-Methylmorpholino	Et	1½
2 : 6-Dimethylmorpholino	Et	1½
O<[CH₂]₄>N·CH₂·CH₂·CPh(*p*-Me·C₆H₄)·COEt		0
O<[CH₂]₄>N·CH₂·CH₂·C(*o*-Me·C₆H₄)₂·COEt		0
$Et_2N·CH_2·CH_2·CH_2·CPh_2·CO_2Et$		0
$Et_2N·CH_2·CH_2·CH_2·CPh_2·COEt$		0
O<[CH₂]₄>N·CH₂·CH₂·CH₂·CPh₂·COEt		0
O<[CH₂]₄>N·CH₂·CH₂·CH₂·CH₂·CPh₂·COEt		0

(*a*) These compounds are listed by Kleiderer *et al.* (*loc. cit.*).
(*b*) See Thorp, Walton, and Ofner (*Nature*, 1947, **159**, 679).
(*c*) See MacDonald, Wolfe, Bergel, Morrison, and Rinderknecht (*loc. cit.*).
(*d*) See Scott, Robbins, and Chen (*Science*, 1946, **104**, 587).
(*e*) The compound was too insoluble to be tested.
(*f*) The quoted activities of these compounds relative to pethidine are on a weight basis.

Attempts to prepare the esters (IX; R = Me, $n = 2$) and (IX; R = Et, $n = 2$) *via* the acid chloride gave rather surprising results. The corresponding cyanides were hydrolysed with concentrated hydrochloric acid at 150°. Treatment of the resulting acids with thionyl chloride

gave, not the expected acid chlorides, but neutral, water-insoluble compounds having the elementary composition of 3 : 3-*diphenyl*-1-*methyl*- (X; R = Me) and -1-*ethyl*-*pyrrolid*-2-*one* (X; R = Et), respectively. In view of the extreme ease of this reaction it is rather surprising that the higher acid chloride shows no tendency at all to cyclise to a piperidone.

The pyrrolidones (X; R = Me) and (X; R = Et) were also prepared by reaction of αα-diphenyl-γ-butyrolactone (XI; for preparation see Part II) with methylamine and ethylamine respectively, in aqueous alcohol; they were found to be identical with the corresponding compounds prepared from the cyanides (VIII).

The conversion of the cyanides (V) into ketones (XII) was accomplished readily in most instances by the use of excess of Grignard reagent. A fairly high temperature (> 80°) was necessary, and the reactions were carried out in toluene at water-bath temperature. With 1 : 1-*di*-o-*tolyl*-3-*morpholinopropyl cyanide* (V; R = $-CH_2 \cdot CH_2 \cdot O \cdot CH_2 \cdot CH_2-$, Ar = *o*-tolyl, *n* = 2) the methyl groups appeared to hinder the reaction; our usual conditions gave a very low yield of the *ketone*, and much unchanged cyanide was recovered.

$$\text{(V.)}\quad R_2N \cdot [CH_2]_n \cdot CAr_2 \cdot CN \xrightarrow{R'MgX} R_2N \cdot [CH_2]_n \cdot CAr_2 \cdot COR' \quad \text{(XII.)}$$

For testing, the compounds were converted, where possible, into hydrochlorides. Very often crystalline hydrochlorides could not be obtained; the compound was then dissolved in an equivalent quantity of hydrochloric acid. Analgesic activity was measured in rats against that of pethidine, two methods being used: (*a*) the thermal radiation method of D'Amour and Smith (*J. Pharm. Exp. Ther.*, 1941, **72**, 74), using the apparatus of Hardy, Wolff, and Goodell (*J. Clin. Invest.*, 1940, **19**, 659) as modified by Thorp (*Brit. J. Pharmacol.*, 1946, **1**, 113); (*b*) the electric grid method of Dodds, Lawson, Simpson, and Williams (*J. Physiol.*, 1945, **104**, 47). Except with the most active compounds, the comparison was made at one fifth the L.D. 50 of both pethidine and the compound under examination.

The relative activities are given in Table I. A complete account of the pharmacological investigation of the compounds described in this and the following paper will be published elsewhere.

Experimental.

(M. p.s are corrected.)

Preparation of Straight-chain ω-Amino-cyanides—Method A.

Preparation of Amino-alcohols.—*2-Dibenzylaminoethanol.* Benzylation of ethanolamine by the method of Rumpf and Kwass (*Bull. Soc. chim.*, 1943, **10**, 347) gave only a 47% yield; the use of solid potassium carbonate in place of sodium hydroxide solution to remove acid formed raised the yield to 61%. The compound boiled at 204—206°/15 mm. and melted at 46—47° (Gabel, *ibid.*, 1934, **1**, 1006, gives b. p. 220—225°/23 mm. and m.p. 45·5—47°).

2-Pyrrolidinoethanol. A solution of 1 : 4-dibromobutane (86·4 g.) in ethanol (100 c.c.) was warmed on the steam-bath, and ethanolamine (73·2 g.) was added gradually at such a rate that the mixture boiled gently. When the addition was complete, the mixture was boiled under reflux for 3 hours. Most of the ethanol was distilled off, and ether was added to the residue. The precipitated oil solidified on being left in the refrigerator, and was filtered off and washed thoroughly with ether. The filtrate and washings were dried (K_2CO_3), the ether was removed, and the residue was distilled. The amino-alcohol boiled at 73—75°/11 mm. (Found: Equiv., 115·9. Calc. for $C_6H_{13}ON$: Equiv., 115·2). Yield 30·8 g.; 67%.

The picrate melted at 86—87° after crystallisation from alcohol (Found: C, 42·3; H, 4·7; N, 16·2. Calc. for $C_6H_{13}ON,C_6H_3O_7N_3$: C, 41·9; H, 4·7; N, 16·3%) (v. Braun, Braunsdorf, and Räth, *Ber.*, 1922, **55**, 1666, give b. p. 187—189° for the base and m. p. 96° for the picrate).

2-Morpholinoethanol. (*a*) The method of Gilman and Woods (*J. Amer. Chem. Soc.*, 1945, **67**, 1843), using ethylene chlorohydrin and morpholine, gave a 91% yield when the period of heating under reflux was extended to 4 hours. (*b*) Ethylene oxide (104 g.) was passed into a boiling mixture of morpholine (180 g.) and anhydrous methanol (35 c.c.) during about 2½ hours. The mixture was boiled for a further 45 minutes and distilled under reduced pressure. 2-Morpholinoethanol boiled at 111—115°/17 mm. (Gilman and Woods, *loc. cit.*, give b. p. 116—119°/21—23 mm.). Yield 230 g.; 85%.

2-(2 : 6-Dimethylmorpholino)ethanol. Di-(2-chloro*iso*propyl) ether (160 g.), ethanolamine (80 g.), and anhydrous potassium carbonate (150 g.) were heated together at 150° for 6 hours. The mixture was extracted with 4 portions (each 100 c.c.) of boiling benzene and the extract dried (K_2CO_3). Removal of the benzene and distillation of the residue, gave the *amino-alcohol* as a colourless liquid, b. p. 109°/10 mm. (Found: N, 8·95. $C_8H_{17}O_2N$ requires N, 8·8%). Yield 117 g.; 79%.

4-Diethylaminobutanol. The method of Smorgonskiĭ and Gol'dfarb (*J. Gen. Chem. Russia*, 1940, **10**, 1113) gave rather poor yields, apparently owing to hydrolysis of the acetyl group during reaction of 4-bromobutyl acetate with diethylamine. The following method was found more satisfactory: a solution of 4-bromobutyl acetate (19·5 g.) and diethylamine (14·6 g.) in dry toluene (25 c.c.) was boiled under reflux for 3 hours. After cooling, diethylamine hydrobromide was filtered off, and washed with toluene. The filtrate and washings were combined, and the toluene was removed under reduced pressure. A solution of sodium hydroxide (20 g.) in alcohol (200 c.c.) was added to the residue, and the mixture was

boiled under reflux for 3 hours. Most of the alcohol was removed, a small amount of water was added, and the solution was extracted thoroughly with ether. The extract was dried (K_2CO_3), the ether was removed, and the residue distilled. 4-Diethylaminobutanol boiled at 103—106°/15 mm. (Smorgonskiĭ and Gol'dfarb, *loc. cit.*, give b. p. 87—90°/8 mm.). Yield 8·5 g.; 59%.

Preparation of Chloro-amines.—Except where otherwise stated the following method was used (cf. Slotta and Behnisch, *Ber.*, 1935, **68**, 754); the amino-alcohol was dissolved in 10 volumes of benzene, and thionyl chloride in about 100% excess was added gradually with occasional shaking to the ice-cooled solution. When the addition was complete, the mixture was boiled under reflux for 2 hours and allowed to cool. In most cases the chloro-amine hydrochloride could be filtered off directly; otherwise the benzene and excess of thionyl chloride were removed, and ether was added to the residue; crystallisation then resulted.

The hydrochlorides were converted into the bases by dissolving in a little water, adding an excess of a solution of sodium hydroxide or potassium carbonate, extracting thoroughly with ether, drying the extract (K_2CO_3), and distilling. In some cases the bases were not isolated; benzene was used in the extraction, and the dried benzene solution was used for the next stage. The bases were always liberated from their hydrochlorides immediately before use.

2-*Di*-n-*butylaminoethyl chloride*. 2-Di-*n*-butylaminoethanol (Burnett, Jenkins, Peet, Dreger, and Adams, *J. Amer. Chem. Soc.*, 1937, **59**, 2248), treated with thionyl chloride as above, gave the crude chloro-amine hydrochloride, m. p. 78—82°, in 92% yield. The base, obtained in 87% yield, boiled at 106—110°/18 mm. (Blicke and Maxwell, *ibid.*, 1942, **64**, 428, give b.p. 114—115°/23 mm.).

2-*Dibenzylaminoethyl chloride*. The *hydrochloride* (98% yield) melted at 191—192° after crystallisation from alcohol–ether (Found: N, 4·5; Cl, 23·3. $C_{16}H_{18}NCl,HCl$ requires N, 4·7; Cl, 23·9%). (Eisleb, U.S.P. 1,949,247, gives m. p. 192° but quotes no analysis.) The *base*, obtained in 80% yield, boiled at 194—195°/12 mm. (Found: N, 5·7; Cl, 14·2. $C_{16}H_{18}NCl$ requires N, 5·4; Cl 13·65%).

2-*Pyrrolidinoethyl chloride*. The hydrochloride (yield 87%) melted at 168—170° after crystallisation from acetone. The base, obtained in 82% yield, boiled at 55—56°/11 mm. The compound was characterised as its *picrate*, which melted with decomposition at 316° after crystallisation from acetone (Found: N, 15·7. $C_6H_{12}NCl,C_6H_3O_7N_3$ requires N, 15·5%).

2-*Piperidinoethyl chloride*. The crude hydrochloride, obtained in 97% yield from 2-piperidinoethanol (Vassiliades, *Bull. Soc. chim.*, 1937, **4**, 1131), melted at 228—230° (Blicke and Maxwell, *loc. cit.*, give m. p. 229—231°). The base (yield 53%) boiled at 79—80°/13 mm. (Gilman and Woods, *loc. cit.*, give b. p. 36—38°/0·5 mm.).

2-(2 : 6-*Dimethylmorpholino*)*ethyl chloride*. The *hydrochloride* (89% yield) melted at 240—244° (decomp.) after crystallisation from alcohol (Found: N, 7·1; Cl, 32·9. $C_8H_{16}ONCl,HCl$ requires N, 6·5; Cl, 33·1%). The *base*, obtained in 72% yield, boiled at 94°/12 mm. (Found: C, 54·1; H, 9·3; N, 8·5. $C_8H_{16}ONCl$ requires C, 54·1; H, 9·1; N, 7·9%).

4-*Diethylaminobutyl chloride*. A solid hydrochloride could not be isolated; when an aqueous solution of the crude hydrochloride was treated with alkali and extracted with ether, the extract rapidly deposited an oil which solidified when kept. This compound was hygroscopic but it was converted into NN-*diethylpyrrolidinium picrate* which melted at 273—273·5° (decomp.) (Found: N, 15·6. $C_8H_{17}N,C_6H_3O_7N_3$ requires N, 15·7%).

An attempt to use a dry benzene extract of the base in the next stage was unsuccessful, even though the extract was left for a very short time only.

Preparation of Amino-cyanides.—The majority of the compounds were prepared by the following general method; variations from this method are described under the individual compounds.

Diphenylmethyl cyanide (Hoch, *Compt. rend.*, 1933, **197**, 770) (0·1 g.-mol.) was dissolved in dry benzene (150 c.c.), sodamide (0·103 g.-mol.) was added, and the mixture was stirred at room temperature till no further darkening occurred. A solution of the appropriate chloro-amine (0·1 g. mol.) in dry benzene (150 c.c.) was added, and the mixture was stirred overnight at room temperature. The solution was extracted with successive portions of 2N-hydrochloric acid (about 0·3 g.-mol. in all), and the combined aqueous layers, together with the sparingly soluble hydrochloride which usually separated as a third, lowest layer, were made strongly alkaline. The resulting oil was extracted with ether or benzene, the extract dried (K_2CO_3), the solvent removed, and the residue purified by distillation or crystallisation.

3-*Dimethylamino*-1 : 1-*diphenylpropyl cyanide*. Prepared in 70% yield from 2-dimethylaminoethyl chloride (Slotta and Behnisch, *loc. cit.*), the cyanide distilled at 150—152°/0·8 mm. as a colourless oil. It was characterised as the *hydrochloride*, which separated from ethanol–ether as colourless crystals, m. p. 200—201° (Found: C, 71·7; H, 7·0; N, 9·6; Cl, 12·1. $C_{18}H_{20}N_2,HCl$ requires C, 71·9; H, 7·0; N, 9·3; Cl, 11·8%).

3-*Diethylamino*-1 : 1-*diphenylpropyl cyanide*. Prepared in 70—78% yield from 2-diethylaminoethyl chloride hydrochloride (Slotta and Behnisch, *loc. cit.*), without isolation of the base, the *cyanide* distilled as a colourless viscous oil at 165°/1 mm. (Found: C, 81·6; H, 8·3; N, 9·8. $C_{20}H_{24}N_2$ requires C, 82·15; H, 8·3; N, 9·6%).

3-*Di*-n-*butylamino*-1 : 1-*diphenylpropyl cyanide*. The reaction of 2-di-*n*-butylaminoethyl chloride with diphenylmethyl cyanide was carried out by the general method but the method of isolation had to be modified. After being stirred overnight the benzene solution was extracted with hydrochloric acid, the amino-cyanide in this case remaining in the benzene layer. The benzene solution was dried (K_2CO_3), the solvent removed, and the residue distilled. 3-*Di*-n-*butylamino*-1 : 1-*diphenylpropyl cyanide* boiled at 170—172°/0·25 mm. (Found: C, 83·0; H, 9·8; N, 8·0. $C_{24}H_{32}N_2$ requires C, 82·7; H, 9·3; N, 8·0%). Yield 66%.

3-*Dibenzylamino*-1 : 1-*diphenylpropyl cyanide*. A solution of diphenylmethyl cyanide (52 g.) in dry benzene (400 c.c.) was treated with sodamide (11 g.), and the mixture was boiled under reflux with stirring till no further solid separated. A solution of 2-dibenzylaminoethyl chloride (liberated from 76 g. of the hydrochloride) in benzene (400 c.c.) was added, and the mixture was boiled under reflux with stirring for 16 hours. After cooling, the mixture was washed with water, and dried over potassium carbonate. Dry hydrogen chloride was passed into the warm solution, and excess of the gas was

eliminated by boiling. Addition of petroleum (b. p. 60—80°) and cooling caused the separation of 3-*dibenzylamino*-1 : 1-*diphenylpropyl cyanide hydrochloride*, which melted at 169—171·5° after recrystallisation from benzene (Found : N, 6·3; Cl, 7·6. $C_{30}H_{28}N_2$,HCl requires N, 6·2; Cl, 7·8%). Yield 61 g., 53%, based on the chloro-amine hydrochloride.

The *base*, prepared from the hydrochloride in 92% yield, melted at 60·5—61·5° after crystallisation from petroleum (Found : C, 86·2; H, 6·7; N, 6·85. $C_{30}H_{28}N_2$ requires C, 86·5; H, 6·8; N, 6·7%).

1 : 1-*Diphenyl*-3-*pyrrolidinopropyl cyanide*. Diphenylmethyl cyanide (17·4 g.) was converted into the sodio-derivative by boiling under reflux with sodamide (3·6 g.) in dry benzene (150 c.c.) with stirring until the separation of solid was complete. 2-Pyrrolidinoethyl chloride (11·7 g.) in benzene (20 c.c.) was added gradually, and the mixture was stirred overnight at room temperature. The *product* melted at 71·5—72·5° after crystallisation from petroleum (b. p. 60—80°) (Found : C, 83·0; H, 7·3; N, 9·6. $C_{30}H_{32}N_2$ requires C, 82·7; H, 7·6; N, 9·7%). Yield, 84% based on chloro-amine.

1 : 1-*Diphenyl*-3-*piperidinopropyl cyanide*. Prepared by the general method in 57% yield, the *cyanide* melted at 70—71° after crystallisation from petroleum (b. p. 60—80°) (Found : C, 82·8; H, 8·2; N, 9·2. $C_{31}H_{34}N_2$ requires C, 82·8; H, 7·95; N, 9·2%). (Thorp, Walton, and Ofner, *Nature*, 1947, **159**, 679, give m. p. 73° but do not quote analytical figures.)

1 : 1-*Diphenyl*-3-*morpholinopropyl cyanide*. 2-Morpholinoethyl chloride (Mason and Block, *J. Amer. Chem. Soc.*, 1940, **62**, 1443) on reaction with diphenylmethyl cyanide gave 1 :1-*diphenyl*-3-*morpholinopropyl cyanide* in 56% yield. After crystallisation from petroleum (b. p. 40—60°) the cyanide melted at 82—82·5° (Found : C, 78·7; H, 7·2; N, 9·1. $C_{30}H_{32}ON_2$ requires C, 78·4; H, 7·2; N, 9·1%).

1 : 1-*Diphenyl*-3-(2 : 6-*dimethylmorpholino*)*propyl cyanide*. The *cyanide* (yield 48%) crystallised from petroleum (b. p. 60—80°) in colourless plates, m. p. 67—72° (Found : C, 78·7; H, 7·8; N, 8·2. $C_{32}H_{36}ON_2$ requires C, 79·0; H, 7·8; N, 8·4%). The *hydrochloride* melted at 190—194° (decomp.) after crystallisation from acetone–ether (Found : N, 7·7. $C_{32}H_{36}ON_2$,HCl requires N, 7·6%).

4-*Diethylamino*-1 : 1-*diphenylbutyl cyanide*. Reaction of 3-diethylaminopropyl chloride (Slotta and Behnisch, *loc. cit.*) with diphenylmethyl cyanide by the general method gave only a 50% yield of the desired compound, much of the starting materials being recovered unchanged. By preparing sodiodiphenylmethyl cyanide in boiling benzene, and heating under reflux for 3 hours after the addition of the chloro-amine, the yield was raised to 75%. 4-Diethylamino-1 : 1-diphenylbutyl cyanide boiled at 160—163°/0·3 mm. The *hydrochloride* melted at 158—160° (Found : C, 73·5; H, 7·8; N, 8·6; Cl, 10·9. $C_{31}H_{36}N_2$,HCl requires C, 73·55; H, 7·9; N, 8·2; Cl, 10·3%).

1 : 1-*Di*-o-*tolyl*-3-*morpholinopropyl cyanide*. A solution of di-*o*-tolylmethyl cyanide (Fuson and Rachlin, *J. Amer. Chem. Soc.*, 1942, **64**, 1567) (5·27 g.) in benzene (40 c.c.) was treated with sodamide (1 g.), and the mixture was boiled under reflux with stirring until the separation of solid was complete (about 1½ hrs.). To the cooled suspension was added gradually a solution of 2-morpholinoethyl chloride (3·8 g.) in dry benzene (10 c.c.), and the mixture was boiled under reflux with stirring for 3 hours. The *product* melted at 138—139° after crystallisation from petroleum (b. p. 60—80°) (Found : C, 78·7; H, 7·95; N, 8·6. $C_{32}H_{36}ON_2$ requires C, 79·0; H, 7·8; N, 8·4%). Yield 5·5 g., 70%.

Preparation of Straight-chain ω-Amino-cyanides. Method B.

3-*Chloro*-1 : 1-*diphenylpropyl cyanide*. A solution of diphenylmethyl cyanide (19·3 g.) in dry benzene (140 c.c.) was treated with sodamide (4 g.), and the mixture was boiled under reflux with stirring until the separation of solid was complete (about 1 hour). The mixture was cooled to room temperature, and ethylene dichloride (17·2 g.) was added. The mixture was stirred, heated under reflux for 4 hours, and, after cooling, was washed with water and dried. Removal of the benzene left an oil which boiled between 130° and 140°/0·4 mm., and solidified on standing (18 g.; 70% yield). Crystallisation from petroleum (b. p. 40—60°) gave the *cyanide* in large colourless crystals, m. p. 51·5—53° (Found : C, 75·7; H, 5·5; N, 5·6; Cl, 14·3. $C_{16}H_{14}NCl$ requires C, 75·1; H, 5·5; N, 5·5; Cl, 13·9%). The residue in the distillation flask was crystallised from benzene, giving 1 : 4-*dicyano*-1 : 1 : 4 : 4-*tetraphenylbutane*, m. p. 200—204° (Found : C, 87·3; H, 6·0; N, 6·7. $C_{30}H_{24}N_2$ requires C, 87·4; H, 5·9; N, 6·8%).

Prolonged treatment of the chloro-cyanide with piperidine in benzene, toluene, or aqueous ethanol containing sodium hydrogen carbonate gave only traces of 1 : 1-diphenyl-3-piperidinopropyl cyanide, the starting materials being largely recovered.

3-*Bromo*-1 : 1-*diphenylpropyl cyanide*. Diphenylmethyl cyanide (96·5 g.) was treated with sodamide (20 g.) in boiling benzene (750 c.c.) as above, and, after cooling, ethylene dibromide (75 c.c.) was added. The mixture was boiled under reflux with stirring for 3½ hours, cooled, and washed with water. The benzene solution was dried, the solvent removed, and the residue heated on the water-bath under reduced pressure to remove excess of ethylene dibromide. On trituration with petroleum, the oily residue solidified, and was filtered off and dried. Yield 111—120 g., 74—80%. The *solid*, m. p. 60—63°, was pure enough for use in the next stage, but it could be crystallised from petroleum with some difficulty, and then melted at 68·5—70° (Found : C, 64·0; H, 4·8; N, 4·8; Br, 26·5. $C_{16}H_{14}NBr$ requires C, 64·0; H, 4·7; N, 4·7; Br, 26·6%).

3-*Di*-n-*propylamino*-1 : 1-*diphenylpropyl cyanide*. A mixture of 3-bromo-1 : 1-diphenylpropyl cyanide (30 g.) and dipropylamine (20 g.) was boiled under reflux for 16 hours. After cooling, ether was added, and dipropylamine hydrobromide was filtered off. The filtrate was evaporated to dryness, and the residue was dissolved in hot benzene, and treated with hydrogen chloride. The excess of hydrogen chloride was boiled off and the solution allowed to cool; 3-di-*n*-propylamino-1 : 1-diphenylpropyl cyanide hydrochloride then separated, and had m. p. 84—85° after crystallisation from benzene–petroleum (b. p. 60—80°). Yield 24 g., 67%. The *base* (79% yield) boiled at 179—180°/1·2 mm. (Found : C, 82·4; H, 8·5; N, 8·6. $C_{22}H_{28}N_2$ requires C, 82·4; H, 8·8; N, 8·7%).

3-*Benzylmethylamino*-1 : 1-*diphenylpropyl cyanide*. 3-Bromo-1 : 1-diphenylpropyl cyanide (15 g.) and benzylmethylamine (12 g.) were heated together on the water-bath overnight. Ether was added,

the precipitate of benzylmethylamine hydrobromide filtered off, and the filtrate extracted with an excess of 2N-hydrochloric acid. The acid extract was made strongly alkaline, and the oil extracted with ether. The ether solution was dried, the ether removed, and the residue distilled, giving the amino-cyanide, b. p. 190—196°/0·3—0·4 mm. Yield 11·4 g., 67%. The *hydrochloride*, prepared in benzene and crystallised from acetone–ether, melted at 147·5—150° (Found: C, 76·3; H, 6·6; N, 7·2; Cl, 9·1. $C_{24}H_{24}N_2$,HCl requires C, 76·5; H, 6·7; N, 7·4; Cl, 9·4%).

1 : 1-*Diphenyl*-3-*piperidinopropyl cyanide*. 3-Bromo-1 : 1-diphenylpropyl cyanide (3 g.), piperidine (2 c.c.), and toluene (20 c.c.) were boiled under reflux for 20 hours. Piperidine hydrobromide was filtered off, and the filtrate was extracted with an excess of 2N-hydrochloric acid. The acid extract was made strongly alkaline, and extracted with ether. Removal of the ether left an oil which solidified, and melted at 70—71° after crystallisation from petroleum. Yield 1·9 g., 63%.

The replacement of toluene by xylene in the above experiment gave a yield of 70%. When the reaction was carried out with only 1 mol. of piperidine, with sodium hydrogen carbonate to neutralise acid formed, and aqueous alcohol as solvent, a yield of 60% of the amino-cyanide resulted.

1 : 1-*Diphenyl*-3-(2-*methylpiperidino*)*propyl cyanide*. A mixture of 3-bromo-1 : 1-diphenylpropyl cyanide (22·3 g.), 2-methylpiperidine (14·9 g.), and xylene (150 c.c.) was boiled under reflux for 24 hours. The product (61% yield) was not distilled but was converted into the *hydrochloride* which melted at 188—189° after crystallisation from ethyl acetate (Found: N, 7·4. $C_{22}H_{26}N_2$,HCl requires N, 7·9%).

1 : 1-*Diphenyl*-3-(3-*methylpiperidino*)*propyl cyanide*. Prepared as above, the *base* boiled at 178—180°/0·1 mm. (Found: C, 83·3; H, 8·1; N, 8·4. $C_{22}H_{26}N_2$ requires C, 83·0; H, 8·2; N, 8·8%). Yield 57%.

1 : 1-*Diphenyl*-3-(4-*methylpiperidino*)*propyl cyanide*. The *cyanide*, prepared in 59% yield by the method used for the isomeric compounds, boiled at 184—185°/0·025 mm., and had m. p. 61—62° after crystallisation from aqueous ethanol (Found: N, 8·4%). The *hydrochloride* melted at 189·5—191° after crystallisation from acetone–ether (Found: N, 7·6%).

1 : 1-*Diphenyl*-3-(2 : 6-*dimethylpiperidino*)*propyl cyanide*. 2 : 6-Dimethylpiperidine was prepared by reduction of 2 : 6-dimethylpyridine with sodium and alcohol; the two forms were separated by treatment of the hydrochlorides with acetone (Marcuse and Wolffenstein, *Ber.*, 1899, **32**, 2525). The major portion of the salt was the high-melting form to which these workers assigned the *meso*-structure. The base obtained from this hydrochloride was used in the reaction with 3-bromo-1 : 1-diphenylpropyl cyanide.

3-Bromo-1 : 1-diphenylpropyl cyanide (23·8 g.) and 2 : 6-dimethylpiperidine (18 g.) were heated in an oil-bath at 180—200° for 22 hours. After cooling, ether was added, and the precipitate of dimethylpiperidine hydrobromide was filtered off. The ether was removed, and the residue heated for a further 6 hours. The product boiled at 170—172°/0·04 mm. The *hydrochloride* melted at 239—243° after crystallisation from ethyl acetate (Found: N, 8·0; Cl, 9·4. $C_{23}H_{28}N_2$,HCl requires N, 7·6; Cl, 9·6%). Yield 11·5 g., 44%.

1 : 1-*Diphenyl*-3-*morpholinopropyl cyanide*. 3-Bromo-1 : 1-diphenylpropyl cyanide (75 g.) and morpholine (45 g.) were heated on the water-bath for 16 hours. Ether was added, morpholine hydrobromide was filtered off, and the filtrate was worked up. The amino-cyanide (59 g., 77% yield) melted at 82° after crystallisation from petroleum.

1 : 1-*Diphenyl*-3-(2-*methylmorpholino*)*propyl cyanide*. 3-Bromo-1 : 1-diphenylpropyl cyanide (15 g.) and 2-methylmorpholine (Cottle, Jeltsch, Stoudt, and Walters, *J. Org. Chem.*, 1946, **11**, 286) (10 g.) were heated on the water-bath for 16 hours; the *product* boiled at 160°/0·025 mm. (Found: N, 8·7. $C_{21}H_{24}ON_2$ requires N, 8·75%). Yield 11 g., 69%. The hydrochloride melted at 132—135° after crystallisation from ethyl acetate–ether (Found: N, 8·0; Cl, 9·8. $C_{21}H_{24}ON_2$,HCl requires N, 7·85; Cl, 9·9%).

3-*Bromo*-1-*phenyl*-1-p-*tolylpropyl cyanide*. Phenyl-*p*-tolylmethyl cyanide (Hoch, *loc. cit.*) (10·35 g.) was dissolved in benzene (80 c.c.), sodamide (2 g.) was added, and the mixture was boiled under reflux with stirring till the separation of solid was complete. The suspension was cooled to room temperature, ethylene dibromide (16·45 g.) was added gradually, and the mixture was boiled under reflux with stirring for 3 hours. After cooling, the solution was washed with water, dried, and evaporated. Distillation of the residue gave 3-*bromo*-1-*phenyl*-1-p-*tolylpropyl cyanide* (10·6 g., 68% yield), b. p. 126—136°/0·02 mm. (Found: Br, 25·75. $C_{17}H_{16}NBr$ requires Br, 25·4%).

1-*Phenyl*-1-p-*tolyl*-3-*morpholinopropyl cyanide*. 3-Bromo-1-phenyl-1-*p*-tolylpropyl cyanide (6·7 g.) and morpholine (3·7 g.) were heated on the water-bath for 16 hours. The *product* distilled at 170°/0·02 mm. (Found: N, 8·8. $C_{21}H_{24}ON_2$ requires N, 8·75%). Yield 5·2 g., 76%. The *hydrochloride* melted at 220—224° after crystallisation from acetone–ether (Found: C, 70·4; H, 7·2; N, 8·0; Cl, 9·8. $C_{21}H_{24}ON_2$,HCl requires C, 70·7; H, 7·1; N, 7·85; Cl, 9·9%).

1 : 1-*Diphenyl*-4-*morpholinobutyl cyanide*. Diphenylmethyl cyanide (19·3 g.) was converted into its sodio-derivative by treatment with sodamide (4 g.) and boiling benzene (50 c.c.); the cold suspension was treated with 1 : 3-dibromopropane (35·3 g.), and the mixture was heated under reflux with stirring for 4 hours. After cooling, the mixture was washed with water and dried. The benzene was removed, and excess of dibromopropane distilled off at *ca.* 115°/15 mm. The residual oil was used for the next stage without purification. The 4-*bromo*-1 : 1-*diphenylbutyl cyanide* could be distilled, and then crystallised from petroleum (b. p. 40—60°); it melted at 77—78° (Found: C, 64·9; H, 5·7; Br, 26·2. $C_{17}H_{16}NBr$ requires C, 65·0; H, 5·1; Br, 25·4%).

The crude bromo-compound from the above experiment was heated overnight on the steam-bath with morpholine (20 g.); after cooling, ether was added, morpholine hydrobromide filtered off, and the ether filtrate extracted with an excess of 2N-hydrochloric acid. The oily hydrochloride, which separated, solidified and was filtered off; yield 11 g., 31% based on diphenylmethyl cyanide. On crystallisation from alcohol the 1 : 1-*diphenyl*-4-*morpholinobutyl cyanide hydrochloride* melted at 245—247° (Found: C, 70·4; H, 6·9; N, 7·75; Cl, 10·5. $C_{21}H_{24}ON_2$,HCl requires C, 70·7; H, 7·1; N, 7·85; Cl, 9·9%). The *base* melted at 65—66° after crystallisation from petroleum (b. p. 40—60°) (Found: C, 78·4; H, 7·4; N, 9·0. $C_{21}H_{24}ON_2$ requires C, 78·7; H, 7·55; N, 8·75%).

1 : 1-*Diphenyl*-5-*morpholinoamyl cyanide*. Diphenylmethyl cyanide (19·3 g.) was converted into

its sodio-derivative by means of sodamide (4 g.) in boiling benzene (150 c.c.). After cooling, the suspension was treated with 1 : 4-dibromobutane (37·5 g.). The mixture was boiled under reflux for 4 hours, washed with water, and dried. Benzene was removed and the residue heated at 150° under reduced pressure to remove excess of dibromobutane. The residue (19 g.) was treated with morpholine (17·4 g.) in boiling xylene (50 c.c.) for 2 hours, and the product was worked up in the usual way. 1 : 1-*Diphenyl*-5-*morpholinoamyl cyanide* (10 g., 30% based on diphenylmethyl cyanide) melted at 97—98° after crystallisation from petroleum (b. p. 60—80°) (Found: C, 78·7; H, 7·9; N, 8·2. $C_{22}H_{26}ON_2$ requires C, 79·0; H, 7·8; N, 8·4%).

In one run on the same scale an attempt was made to purify the intermediate bromo-compound. Addition of petroleum to the crude oily material gave a solid (6·5 g.) which melted at 224—228° after crystallisation from benzene–petroleum, and was found by analysis to be 1 : 6-*dicyano*-1 : 1 : 6 : 6-*tetraphenylhexane* (Found: C, 87·4; H, 6·6; N, 6·1. $C_{32}H_{28}N_2$ requires C, 87·2; H, 6·4; N, 6·4%). It was not possible to obtain the pure bromo-compound from the petrol-soluble material.

Preparation of Amino-acids and -esters and Pyrrolidones.

Ethyl 3-*dimethylamino*-1 : 1-*diphenylpropane*-1-*carboxylate*. 3-Dimethylamino-1 : 1-diphenylpropyl cyanide (10 g.), anhydrous ethanol (25 c.c.), concentrated sulphuric acid (8 c.c.), water (0·1 c.c.), and ammonium chloride (1·8 g.) were heated in a sealed tube at 150° for 16 hours. The contents of the tube were diluted with water, made alkaline with 40% sodium hydroxide solution with cooling, and extracted with ether; an intermediate oily layer was run off with the aqueous layer. The extract was dried (K_2CO_3), the ether removed, and the residue distilled. The *ester* (5 g.; 42%) boiled at 150—153°/0·6 mm. (Found: C, 77·2; H, 8·05; N, 4·4; OEt, 14·2. $C_{20}H_{25}O_2N$ requires C, 77·1; H, 8·1; N, 4·5; OEt, 14·5%). The *hydrochloride* melted at 192—194° after crystallisation from acetone–ether (Found: C, 69·4; H, 7·8; N, 4·1; Cl, 10·75. $C_{20}H_{25}O_2N$,HCl requires C, 69·1; H, 7·5; N, 4·0; Cl, 10·2%).

Ethyl 3-*diethylamino*-1 : 1-*diphenylpropane*-1-*carboxylate*. The preparation was similar to that described for the dimethylamino-analogue. The *ester*, obtained in 43% yield, distilled at 165°/0·4 mm. (Found: C, 77·85; H, 9·0; N, 4·4; OEt, 14·0. $C_{22}H_{29}O_2N$ requires C, 77·8; H, 8·6; N, 4·1; OEt, 13·3%) (Bockmühl and Ehrhart, *loc. cit.*, give b. p. 200—202°/5 mm. but quote no analytical figures).

Ethyl 1 : 1-*diphenyl*-3-*piperidinopropane*-1-*carboxylate*. Prepared in 51% yield by the method described above, the *ester* distilled at 170—178°/0·4 mm. and solidified on standing. After crystallisation from petroleum (b. p. 40—60°) it melted at 69—70·5° (Found: C, 78·3; H, 8·0; H, 4·45. $C_{23}H_{29}O_2N$ requires C, 78·6; H, 8·3; N, 4·0%) (Bockmühl and Ehrhart, *loc. cit.*, give b. p. 208—212°/3 mm. but quote no analytical figures).

Ethyl 1 : 1-*diphenyl*-3-*morpholinopropane*-1-*carboxylate*. Prepared as above in 46% yield the *ester* boiled at 175—180°/0·5 mm. and melted at 68·5—70° after crystallisation from petroleum (b. p. 40—60°) (Found: C, 74·7; H, 7·9; N, 4·3. $C_{22}H_{27}O_3N$ requires C, 74·75; H, 7·7; N, 4·0%). The *hydrochloride* melted at 167·5—168·5° after crystallisation from acetone–ether (Found: N, 3·65; Cl, 8·2. $C_{22}H_{27}O_3N$,HCl requires N, 3·6; Cl, 9·1%) (Bockmühl and Ehrhart, *loc. cit.*, give b. p. 218—222°/4 mm. for the base and m. p. 166—167° for the hydrochloride but quote no analytical figures for either).

4-*Diethylamino*-1 : 1-*diphenylbutane*-1-*carboxylic acid*. 4-Diethylamino-1 : 1-diphenylbutyl cyanide (10 g.) and concentrated hydrochloric acid (50 c.c.) were heated at 155—160° in a sealed tube for 16 hours. The contents of the tube were evaporated to dryness under reduced pressure, and the residue was dissolved in the minimum quantity of hot water. The solution was made slightly alkaline with 2N-sodium carbonate solution. On being left in the refrigerator, a solid separated, which was filtered off and crystallised from acetone–ether. The *acid* melted at 141—142° (Found: C, 77·0; H, 8·2; N, 4·4. $C_{21}H_{27}O_2N$ requires C, 77·5; H, 8·4; N, 4·3%). Yield 5·6 g., 53%.

Ethyl 4-*diethylamino*-1 : 1-*diphenylbutane*-1-*carboxylate*. The acid (8·5 g.) was warmed cautiously with thionyl chloride (34 c.c.), and when the reaction became less vigorous the mixture was boiled under reflux for 30 minutes. The excess of thionyl chloride was removed, dry ethanol (45 c.c.) was added, and the mixture was boiled under reflux on the water-bath for 30 minutes. Most of the ethanol was removed, the residue was diluted with water, and an excess of sodium hydroxide solution was added with cooling. The oil was extracted with ether, the extract dried, the ether removed, and the residue distilled. The *ester* (6·8 g., 74%) boiled at 169—174°/0·5 mm. (Found: N, 3·9; OEt, 11·8. $C_{23}H_{31}O_2N$ requires N, 4·0; OEt, 12·75%).

3-*Dimethylamino*-1 : 1-*diphenylpropane*-1-*carboxylic acid*. 3-Dimethylamino-1 : 1-diphenylpropyl cyanide (5 g.) and concentrated hydrochloric acid (25 c.c.) were heated in a sealed tube at 150° for 16 hours. The solution was evaporated to dryness under reduced pressure; the residue was dissolved in a small volume of water, and made slightly alkaline with 2N-sodium carbonate. On cooling in the refrigerator, a solid separated which was filtered off and dried (4·9 g., 91%). On crystallisation from water the *acid* melted at 197—198° (decomp.) (Found: C, 76·3; H, 7·4; N, 4·6. $C_{18}H_{21}O_2N$ requires C, 76·3; H, 7·5; N, 4·9%).

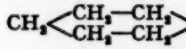
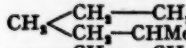
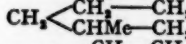
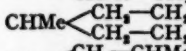
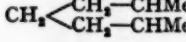
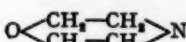
3 : 3-*Diphenyl*-1-*methylpyrrolid*-2-*one*. (*a*) 3-Dimethylamino-1 : 1-diphenylpropane-1-carboxylic acid (1 g.) and thionyl chloride (4 c.c.) were boiled under reflux for 30 minutes. The excess of thionyl chloride was removed, water was added to the residue, and the solid was filtered off. Crystallisation from aqueous alcohol gave white needles, m. p. 146·5—147°, of the *pyrrolidone*. The melting point was not depressed on admixture with a specimen of the compound prepared as described below (Found: C, 80·85; H, 6·8; N, 5·75. $C_{17}H_{17}ON$ requires C, 81·2; H, 6·8; N, 5·6%). Yield 0·85 g., 96%.

(*b*) αα-Diphenyl-γ-butyrolactone (for preparation see following paper) (2 g.), aqueous methylamine (25%, 5 c.c.), and ethanol (20 c.c.) were heated in a sealed tube at 160° for 16 hours. The contents of the tube deposited a crystalline solid, m. p. 146—147°, when left. A further quantity was obtained by concentration of the mother-liquors. On crystallisation from aqueous alcohol the material melted at 146·5—147° (Found: C, 80·8; H, 6·95; N, 5·2%). Yield 1·8 g., 85%.

3-*Diethylamino*-1 : 1-*diphenylpropane*-1-*carboxylic acid*. 3-Diethylamino-1 : 1-diphenylpropyl cyanide (5 g.) and concentrated hydrochloric acid (25 c.c.) were heated overnight in a sealed tube at 140—150°.

TABLE II.

Amino-ketones.

Compound.	Yield, %.	Deriv.	B. p.	Crystaln. solvent.	M. p.	Analysis. Found, %. C.	H.	N.	Cl.	Required, %. C.	H.	N.	Cl.	Notes.
$NMe_2\cdot CH_2\cdot CH_2\cdot CPh_2\cdot COMe$	83	HCl	—	Acetone–ether	186—187·5°	71·6	7·9	4·6	11·3	71·8	7·6	4·4	11·2	
$NMe_2\cdot CH_2\cdot CH_2\cdot CPh_2\cdot COEt$	78	—	154—156°/ 0·8 mm.	—	—	81·6	8·6	4·7	—	81·3	8·5	4·7	—	1
	—	HCl	—	Acetone–ether	173·5—175	72·1	8·0	4·2	10·9	72·4	7·9	4·2	10·7	
$NMe_2\cdot CH_2\cdot CH_2\cdot CPh_2\cdot COPr$	84	—	161—167/ 1 mm.	—	—	82·0	8·6	4·5	—	81·6	8·8	4·5	—	
$NMe_2\cdot CH_2\cdot CH_2\cdot CPh_2\cdot COPh$	89	—	178—184/ 0·3 mm.	—	—	—	—	—	—	—	—	—	—	
	—	HCl	—	Acetone–ether	227—228	76·1	6·9	3·9	9·3	75·9	6·9	3·7	9·3	
$NEt_2\cdot CH_2\cdot CH_2\cdot CPh_2\cdot COEt$	77	—	160—165/ 0·5 mm.	—	—	—	—	4·2	—	—	—	4·3	—	
	—	HCl	—	Acetone–ether	141—143	73·5	8·0	3·9	9·3	73·4	8·4	3·9	9·85	
$NPr_2\cdot CH_2\cdot CH_2\cdot CPh_2\cdot COEt$	65	—	180/0·9 mm.	—	—	82·15	9·4	4·0	—	82·0	9·5	4·0	—	
$NBu_2\cdot CH_2\cdot CH_2\cdot CPh_2\cdot COEt$	70	—	173—180/ 0·5 mm.	—	—	—	—	4·0	—	—	—	3·7	—	2
$N(CH_2Ph)Me\cdot CH_2\cdot CH_2\cdot CPh_2\cdot COEt$	60	—	180—185/ 0·04 mm.	—	—	84·5	7·7	4·2	—	84·05	7·9	3·8	—	
$N(CH_2Ph)_2\cdot CH_2\cdot CH_2\cdot CPh_2\cdot COEt$	54	—	—	Ethanol	86—87	85·3	6·9	3·4	—	85·8	7·4	3·1	—	2
	—	HCl	—	Acetone–ether	162—164 decomp.	79·1	7·0	2·8	7·15	79·4	7·1	2·9	7·3	
	68	—	Subl. 130/ 0·01 mm.	—	68—70	81·8	8·5	4·6	—	82·2	8·5	4·4	—	3
	—	HCl	—	Benzene	80·5—82·5	74·7	8·1	3·4	—	73·8	7·9	3·9	—	
	74	HI	—	Water	197—198	—	—	3·25	—	—	—	3·0	—	4
	—	HCl	—	Acetone–ether	175—176	74·0	8·1	4·15	—	74·3	8·1	3·8	—	
	60	—	169—172/ 0·2 mm.	—	—	82·9	8·8	3·95	—	82·5	8·95	4·0	—	
	60	—	186—188/ 0·5 mm.	—	—	82·9	9·0	3·8	—	82·5	8·95	4·0	—	
	53	—	180—184/ 0·1 mm.	—	—	82·2	8·6	4·3	—	82·5	8·95	4·0	—	
	69	—	166—168/ 0·02 mm.	—	—	82·8	9·05	3·9	—	82·6	9·15	3·9	—	2, 5
	66	—	—	Petrol. (b. p. 40—60°)	100—101	78·4	8·0	4·5	—	78·0	7·8	4·3	—	6
	—	HCl	—	Ethyl acetate	185·5—186·5	70·0	7·5	4·2	9·2	70·1	7·3	3·9	9·9	

O<(CH$_2$—CH$_2$)>(CH$_2$—CH$_2$)N·CH$_2$·CH$_2$·CPh$_2$·COEt	84	—	—	Ethanol	114—115·5	78·3	8·0	4·3	—	78·3	8·1	4·15	—	7
	—	HCl	—	Ethanol–ether	234·5—237	—	—	3·6	10·1	—	—	3·75	9·5	
O<(CH$_2$—CH$_2$)>(CH$_2$—CH$_2$)N·CH$_2$·CH$_2$·CPh$_2$·COPr	50	HCl	—	Ethyl acetate	179·5—181·5	70·7	7·8	3·7	9·4	71·2	7·8	3·6	9·1	
O<(CH$_2$—CH$_2$)>(CHMe—CH$_2$)N·CH$_2$·CH$_2$·CPh$_2$·COEt	65	—	—	Petrol. (b. p. 40—60°)	95—96	78·0	8·5	4·0	—	78·6	8·3	4·0	—	
	—	HCl	—	Acetone–ether	187—189	70·8	7·5	3·6	9·5	71·2	7·8	3·6	9·1	
O<(CHMe—CH$_2$)>(CHMe—CH$_2$)N·CH$_2$·CH$_2$·CPh$_2$·COEt	32	—	—	Petrol. (b. p. 40—60°)	77—81	79·3	8·6	3·95	—	78·9	8·55	3·8	—	8
	—	HCl	—	Acetone–ether	170—174	—	—	3·5	—	—	—	3·5	—	
O<(CH$_2$—CH$_2$)>(CH$_2$—CH$_2$)N·CH$_2$·CH$_2$·CPh(*p*-Me·C$_6$H$_4$)·COEt	61	—	—	Petrol. (b. p. 60—80°)	89—91	78·25	8·2	3·9	—	78·6	8·3	4·0	—	
	—	HCl	—	Acetone–ether	175—177	—	—	3·65	9·2	—	—	3·6	9·1	
O<(CH$_2$—CH$_2$)>(CH$_2$—CH$_2$)N·CH$_2$·CH$_2$·C[*o*-Me·C$_6$H$_4$]$_2$·COEt	—	HCl	—	Ethyl acetate	218—221	—	—	3·7	8·55	—	—	3·5	8·8	9
NEt$_2$·CH$_2$·CH$_2$·CH$_2$·CPh$_2$·COEt	82	—	165—170/0·3 mm.	—	—	81·35	9·2	4·3	—	81·8	9·3	4·15	—	
O<(CH$_2$—CH$_2$)>(CH$_2$—CH$_2$)N·[CH$_2$]$_3$·CPh$_2$·COEt	74	—	—	Acetone–water	98—99	78·85	8·05	4·1	—	78·6	8·3	4·0	—	
	—	HCl	—	Acetone–ether	189—190·5	—	—	3·85	9·2	—	—	3·6	9·1	
O<(CH$_2$—CH$_2$)>(CH$_2$—CH$_2$)N·[CH$_2$]$_4$·CPh$_2$·COEt	79	—	169—173/0·01 mm.	—	—	79·1	8·35	3·6	—	78·9	8·55	3·8	—	

NOTES.

1. In the report of Kleiderer *et al.* (*loc. cit.*) the b. p. of the base is quoted as 186—187°/2·5 mm. and the m. p. of the hydrochloride as 173—175°, but no analytical figures are quoted for either.
2. Owing to the toluene solubility of the salts of these ketones, the entire mixture was made alkaline after decomposition of the Grignard complex and the ketone was extracted with ether.
3. After decomposition of the Grignard complex, the mixture was cooled and the aqueous and toluene layers were decanted from the lowest, gummy layer, which was then treated with alkali and extracted with ether.
The hydrochloride did not give a satisfactory analysis even after repeated crystallisation.
4. The hydriodide crystallised after decomposition of the Grignard complex and cooling.
5. The ketone is believed to have the *meso*-configuration (see above, under the corresponding cyanide).
6. The Grignard reagent was prepared from methyl bromide.
7. The method of isolation was similar to that described in Note 2, but in this instance the free base solidified on basification of the gummy hydriodide and the extraction was omitted.
8. After decomposition of the Grignard complex, the toluene layer was separated and treated with water and ether; the heavy oil was separated and basified with sodium hydroxide. The base was extracted with ether, the dried extract evaporated, and the residue triturated with light petroleum (b. p. 40—60°), when the solid ketone was obtained. The product is presumably a mixture of the (±)- and *meso*-forms.
9. After isolation by the general method, the product was a gum which deposited some unchanged cyanide on trituration with petrol. The filtrate was evaporated and the residue converted into hydrochloride, which was purified by crystallisation from ethyl acetate.

On dilution of the contents of the tube with a little water, a solid separated which was filtered off and dried. The *hydrochloride* was crystallised by dissolving in acetone containing a little ethanol and adding ether, and had m. p. 206—208° (decomp.) (Found: C, 68·8; H, 7·6; N, 4·1; Cl, 9·85. $C_{20}H_{25}O_2N,HCl$ requires C, 69·1; H, 7·5; N, 4·0; Cl, 10·2%). The *3-diethylamino-1 : 1-diphenylpropane-1-carboxylic acid* was liberated from an aqueous solution of the hydrochloride by means of sodium carbonate; after crystallisation from ethanol–ether it melted at 183—184° (decomp.) (Found: N, 4·7. $C_{20}H_{25}O_2N$ requires N, 4·5%). Yield 4·6 g., 86%.

3 : 3-*Diphenyl-1-ethylpyrrolid-2-one.* (*a*) 3-Diethylamino-1 : 1-diphenylpropane-1-carboxylic acid (5 g.) was boiled under reflux for 30 minutes with thionyl chloride (20 c.c.), and the excess of thionyl chloride was removed. Water was added, and the solid was filtered off and crystallised from aqueous alcohol. The *product* (3·8 g.; 89%) melted at 111·5—113°, the m. p. being undepressed on admixture with a specimen prepared as described below (Found: C, 81·5; H, 7·4; N, 5·1. $C_{18}H_{19}ON$ requires C, 81·5; H, 7·2; N, 5·3%).

(*b*) *αα*-Diphenyl-*γ*-butyrolactone (2 g.), aqueous ethylamine (33%, 5 c.c.), and ethanol (20 c.c.) were heated in a sealed tube at 180° for 16 hours. After most of the ethanol had been removed 3 : 3-diphenyl-1-ethylpyrrolid-2-one (2·1 g.; 94%) crystallised as colourless needles which melted at 111·5—112·5° after further crystallisation from aqueous alcohol (Found: C, 81·1; H, 7·0; N, 5·4%).

Conversion of the Amino-cyanides into Amino-ketones.

A Grignard reagent was prepared from magnesium (0·1 g.-mol.) and an alkyl halide (0·1 g.-mol.) in ether (unless otherwise stated the halide used was methyl iodide, ethyl iodide, propyl bromide, or bromobenzene). A solution of the amino-cyanide (0·05 g.-mol.) in dry toluene (*ca.* 35 c.c.) was added, and the ether was removed by distillation until the internal temperature was 95—97°. The residue was heated overnight on the water-bath, and, after cooling, was cautiously decomposed with 2N-hydrochloric acid (200 c.c.). The mixture was heated on the water-bath for 30 minutes to ensure the complete hydrolysis of the intermediate imine. The toluene layer was separated and washed with a little 2N-hydrochloric acid. The combined acid layers, together with a gummy lowest layer which was usually present, were made alkaline with sodium hydroxide, and extracted with ether or, in some cases, benzene. (An alternative method, which avoids the troublesome precipitate of magnesium hydroxide, involves the addition of *ca.* 20 g. of ammonium chloride to each 100 c.c. of the acid solution and basification with ammonia.) The extract was dried (K_2CO_3) and evaporated to dryness, and the residue purified by distillation or crystallisation. The base was converted into the hydrochloride whenever this could be obtained crystalline.

The compounds prepared, together with their physical constants and analytical figures, are listed in Table II. Any departures from the above general method will be found in the notes to the Table.

The authors wish to express their thanks to Mr. G. J. Waller and Mr. R. E. H. Swayne for technical assistance.

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[*Received, May 14th,* 1948.]

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114. *Analgesics. Part II. The Synthesis of Amidone and Some of its Analogues.*

BY J. ATTENBURROW, J. ELKS, B. A. HEMS, and (MISS) K. N. SPEYER.

Treatment of 1-chloro-2-dimethylaminopropane with diphenylmethyl cyanide in the presence of sodamide gave a mixture of compounds, from which 3-dimethylamino-1:1-diphenylbutyl cyanide (II) was isolated in 36% overall yield. Amidone (III) was obtained from (II) by treatment with ethylmagnesium iodide. Both 1-chloro-2-morpholinopropane and 2-chloro-1-morpholinopropane, on reaction with diphenylmethyl cyanide, gave a mixture of 1 : 1-diphenyl-3-morpholinobutyl cyanide (VIII) and 1 : 1-diphenyl-3-morpholino*iso*butyl cyanide (XI), both of which have been converted into the corresponding ethyl ketones.

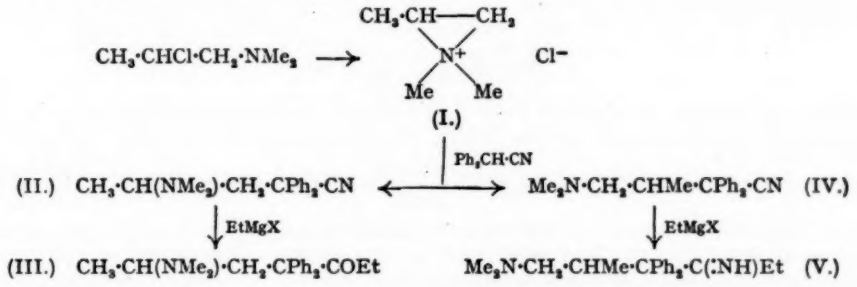
Treatment of diphenylmethyl cyanide with ethylene oxide or propylene oxide gave lactones instead of the hydroxy-cyanides required. Attempts to prepare the cyanide (VIII) by addition of hydrogen bromide or hydrogen iodide to 1 : 1-diphenylbut-3-enyl cyanide (XII) and reaction of the product with morpholine gave the required compound, but only in poor yield. Attempts to reduce selectively the double bond of 3-bromo-1 : 1-diphenylbut-3-enyl cyanide (XXI) were unsuccessful.

THE preparation in Germany of 6-dimethylamino-4 : 4-diphenylheptan-3-one (III; amidone) and the clinical testing of the compound as an analgesic were referred to in Part I. The German method of preparation, as described by Kleiderer *et al.* (Report No. 981, Office of the Publication Board, Department of Commerce, Washington, D.C.) involves the reaction of 2-chloro-1-dimethylaminopropane with diphenylmethyl cyanide in the presence of sodamide, and treatment of the resulting basic cyanide with ethylmagnesium bromide. A rearrangement

is clearly involved in this synthesis, since the product to be expected is 6-dimethylamino-4 : 4-diphenyl-5-methylhexan-3-one, and several workers have studied the reaction.

Schultz, Robb, and Sprague (*J. Amer. Chem. Soc.*, 1947, **69**, 2454) showed that the reaction of 2-chloro-1-dimethylaminopropane with diphenylmethyl cyanide gave roughly equal quantities of 3-dimethylamino-1 : 1-diphenylbutyl cyanide (II) and 3-dimethylamino-1 : 1-diphenyl-*iso*butyl cyanide (IV). The cyanide (II) reacted with ethylmagnesium bromide to give amidone, whereas the cyanide (IV) gave an imine (V), which was not hydrolysed under normal conditions. This imine has, however, been converted into the corresponding ketone by prolonged boiling with 20% hydrochloric acid (Easton, Gardner, and Stevens, *ibid.*, p. 976).

In order to explain the rearrangement, Schultz, Robb, and Sprague (*loc. cit.*) suggested that, under the conditions of reaction, the chloro-amine cyclised to the ethyleneiminium salt (I) which could then be opened in either of two ways :



Evidence that the rearrangement does occur during this stage and not, as suggested by Brode and Hill (*ibid.*, p. 724), during the preparation of the chloro-amines, has very recently been published by Schultz and Sprague (*ibid.*, 1948, **70**, 48) who showed that the chloro-amines prepared from 2-dimethylaminopropan-1-ol and from 1-dimethylaminopropan-2-ol were distinct compounds, no interconversion occurring at normal temperatures, but that each of these chloro-amines gave a similar mixture of cyanides (II) and (IV) on reaction with diphenylmethyl cyanide.

An alternative synthesis of the cyanide (II) has recently been described by Easton, Gardner, and Stevens (*ibid.*, 1947, **69**, 2941), and is referred to elsewhere in this paper.

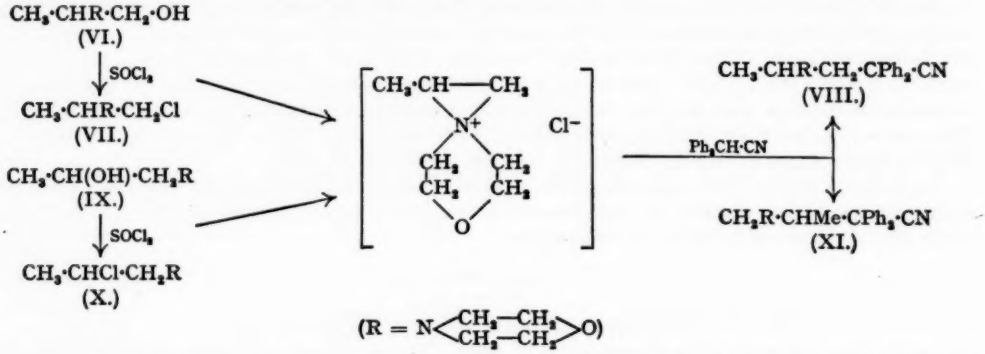
We have prepared the cyanide (II) as follows. 2-Aminopropan-1-ol was methylated with formaldehyde and formic acid, and the resulting 2-dimethylaminopropan-1-ol was treated with thionyl chloride in benzene. The hydrochloride so obtained gave a picrate melting at 158·5—161°, slightly lower, that is, than the melting point (166—167°) found by Schultz and Sprague (*loc. cit.*) for the picrate of 1-chloro-2-dimethylaminopropane. Further, a sample of the distilled base gave a picrate melting at the same temperature, in contradiction to the results of Schultz and Sprague, who found that the base isomerised on distillation, and then gave a picrate, m. p. 101—103°, identical with that prepared from 2-chloro-1-dimethylaminopropane. The undistilled 1-chloro-2-dimethylaminopropane reacted with diphenylmethyl cyanide in the presence of sodamide to give a solid product in 71% yield. Crystallisation from aqueous alcohol gave the pure cyanide (II) in 36% overall yield; no attempt was made to isolate the cyanide (IV) from the mother-liquors. [Schultz and Sprague, *loc. cit.*, using potassium *tert.*-butoxide in place of sodamide, and removing cyanide (IV) from the product by washing with ice-cold hexane, obtained a 40% yield.] Reaction of (II) with an excess of ethylmagnesium iodide in toluene gave amidone (III).

The high analgesic activity of 4 : 4-diphenyl-6-morpholinohexan-3-one as compared with its dimethylamine analogue (see Part I) made it desirable to prepare 4 : 4-*diphenyl-6-morpholino-heptan-3-one*, the morpholine analogue of amidone.

2-*Morpholinopropan*-1-*ol* was prepared by a Bouveault–Blanc reduction of *ethyl α-morpholino-propionate* or, more conveniently, by reaction of 2-aminopropan-1-ol with di-(2-chloroethyl) ether. 1-Chloro-2-morpholinopropane (VII) reacted with sodiodiphenylmethyl cyanide to give a mixture of two isomeric cyanides melting at 140—141° (*A*) and 107—108° (*B*); the mixture contained about 40% of (*A*) and 60% of (*B*). A similar mixture resulted when 1-morpholino-propan-2-ol (IX), prepared from propylene oxide and morpholine, was subjected to the same series of reactions.

The two chloro-amines appeared to be distinct compounds, samples of the distilled bases giving picrates with fairly sharp and quite different melting points. Hence, the rearrangement

would again seem to occur during reaction with diphenylmethyl cyanide, an ethyleneiminium salt probably being transitorily formed during the reaction.



Cyanides (*A*) and (*B*) were shown to be 1 : 1-*diphenyl*-3-*morpholino*isobutyl *cyanide* (XI) and 1 : 1-*diphenyl*-3-*morpholinobutyl cyanide* (VIII), respectively, by the following syntheses :

$$CH_3\cdot CH(OH)\cdot CH_2Cl \longrightarrow CH_3\cdot CHBr\cdot CH_2Cl \xrightarrow[NaNH_2]{Ph_2CH\cdot CN} CH_2Cl\cdot CHMe\cdot CPh_2\cdot CN \xrightarrow[150°]{\text{morpholine}} (XI)$$

1-Chloropropan-2-ol was converted into 1-chloro-2-bromopropane which, on reaction with sodiodiphenylmethyl cyanide and treatment of the crude product with morpholine, gave compound (XI), identical with cyanide (*A*).

$$CH_2{:}CH\cdot CH_2Cl \xrightarrow[NaNH_2]{Ph_2CH\cdot CN} \underset{(XII.)}{CH_2{:}CH\cdot CH_2\cdot CPh_2\cdot CN} \xrightarrow[AcOH]{HBr} CH_3\cdot CHBr\cdot CH_2\cdot CPh_2\cdot CN \xrightarrow{\text{morpholine}} (VIII)$$

1 : 1-Diphenylbut-3-enyl cyanide (XII) was readily prepared by the reaction of sodiodiphenylmethyl cyanide with either allyl chloride or allyl bromide. (The same compound has recently been reported both by Easton, Gardner, and Stevens, *ibid.*, 1947, **69**, 2941, and by Schultz, Robb, and Sprague, *loc. cit.*, the latter workers using potassium *tert.*-butoxide as condensing agent.) Hydrogen bromide was added in acetic acid at 120° in the presence of diphenylamine, and reaction of the crude product with morpholine gave a small yield of cyanide (*B*). The ambiguity in the mode of addition of hydrogen bromide to the double bond does not affect the validity of the proof of structure, since, apart from the improbability of either cyanide (*A*) or cyanide (*B*) being 1 : 1-diphenyl-4-morpholinobutyl cyanide, this last compound is known to have different properties from either of the cyanides (*A*) and (*B*) (see Part I).

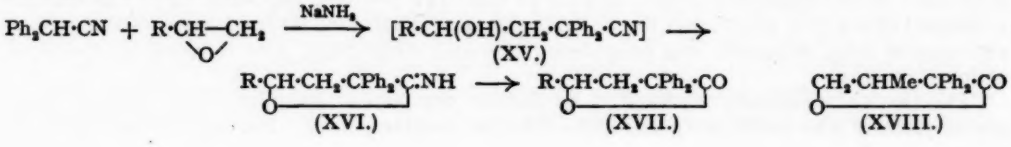
Cyanide (*B*) (VIII) was readily converted into 4 : 4-*diphenyl*-6-*morpholinoheptan*-3-*one* by treatment with ethylmagnesium iodide. Under the same conditions, cyanide (*A*) (XI) gave rise

$$(XI) \xrightarrow{EtMgI} \underset{(XIII.)}{O{<}[CH_2]_4{>}N\cdot CH_2\cdot CHMe\cdot CPh_2\cdot C(:NH)Et} \xrightarrow{HCl} \underset{(XIV.)}{O{<}[CH_2]_4{>}N\cdot CH_2\cdot CHMe\cdot CPh_2\cdot COEt}$$

to the *imine* (XIII) which could be hydrolysed to 4 : 4-*diphenyl*-6-*morpholino*-5-*methylhexan*-3-*one* (XIV) by vigorous treatment with concentrated hydrochloric acid (cf. Easton, Gardner, and Stevens, *loc. cit.*, p. 976).

The very high analgesic activity of 4 : 4-diphenyl-6-morpholinoheptan-3-one made it desirable to find a method of synthesis that would avoid the formation of mixtures, and the remainder of this paper deals with our attempts to devise such a synthesis.

It was hoped that it might be possible to prepare 3-hydroxy-1 : 1-diphenylbutyl cyanide (XV; R = Me) by the reaction of propylene oxide with diphenylmethyl cyanide. Preliminary experiments with ethylene oxide indicated that, in the presence of sodamide or sodium ethoxide in benzene, cyclisation occurred with the formation of *αα-diphenyl-γ-butyrolactone* (XVII; R = H), presumably *via* the imino-compound (XVI; R = H). Alcoholic sodium ethoxide was ineffective as a condensing agent.



Reaction of propylene oxide with diphenylmethyl cyanide in the presence of sodamide in benzene gave the lactone (XVII; R = Me); that this compound was (XVII; R = Me) rather than (XVIII) is shown by its formation from 1 : 1-diphenylbut-3-enyl cyanide and hydrobromic acid (see below). In one preparation of the lactone, a small quantity of the hydrochloride of the imine (XVI; R = Me) was isolated. It was very rapidly hydrolysed by warm dilute hydrochloric acid to the lactone. The preparation of the imine (XVI; R = Me) and the lactone (XVII; R = Me) has recently been described by Easton, Gardner, and Stevens (*loc. cit.*, p. 2941), and by Schultz, Robb, and Sprague (*loc. cit.*).

Some attempts were made to open the ring of the lactones as a preliminary to converting them into basic cyanides of the required type, but they were recovered unchanged after treatment with alcoholic sulphuric acid or a mixture of 48% hydrobromic acid and concentrated sulphuric acid. Since the completion of this work, Easton, Gardner, and Stevens (*loc. cit.*, p. 2941) have shown that the imine (XVI; R = Me) reacts with phosphorus trichloride and phosphorus tribromide to give 3-chloro- and 3-bromo-1 : 1-diphenylbutyl cyanide respectively.

The addition of hydrogen bromide to 1 : 1-diphenylbut-3-enyl cyanide (XII) has been described above. Attempts to increase the yield of 3-bromo-1 : 1-diphenylbutyl cyanide by heating the unsaturated compound with 50% hydrogen bromide in acetic acid at 120° for 48 hours gave the lactone (XVII; R = Me) as the sole product. Attempts to carry out the reaction without a solvent at 120°, or in a variety of solvents under various conditions gave products that, on treatment with morpholine, yielded very small quantities of 1 : 1-diphenyl-3-morpholinobutyl cyanide.

Reaction of (XII) with hydrogen iodide in acetic acid at 80° gave a crude iodine-containing compound which reacted with morpholine in xylene solution to give the compound (VIII) in about 20% overall yield. A wide range of reaction conditions was tried, but in every instance the yield was considerably less than this. Neither benzoyl peroxide nor ascaridole had any influence on the reaction at room temperature.

1 : 1-Diphenylbut-3-enyl cyanide (XII) readily yielded 3 : 4-*dichloro-* and 3 : 4-*dibromo-*1 : 1-*diphenylbutyl cyanide* on reaction with chlorine and bromine, respectively, in chloroform solution. (Schultz, Robb, and Sprague, *loc. cit.*, have recently reported that they were unable to add bromine to the unsaturated cyanide dissolved in carbon tetrachloride.) Both of these dihalides were treated with morpholine in the hope that the 3-halogeno-atom might react selectively, but the basic product consisted solely of 1 : 1-*diphenyl*-3 : 4-*dimorpholinobutyl cyanide*, even when only 2 mols. of morpholine were employed.

Reaction of 2-chloro-1-bromopropane with sodiodiphenylmethyl cyanide gave 3-chloro-1 : 1-diphenylbutyl cyanide (XIX) in fair yield, and reaction with morpholine at 150° gave the desired compound (VIII), but only in about 25% yield.

$$CH_3{\cdot}CHCl{\cdot}CH_2Br \xrightarrow[NaNH_2]{Ph_2CH{\cdot}CN} \underset{\text{(XIX.)}}{CH_3{\cdot}CHCl{\cdot}CH_2{\cdot}CPh_2{\cdot}CN} \xrightarrow{\text{morpholine}} \text{(VIII)}$$

The poor yields obtained in the reaction of 3-halogeno-1 : 1-diphenylbutyl cyanides are in line with the results of Easton, Gardner, and Stevens (*loc. cit.*, p. 2941), who found that the chloro- and bromo-compounds gave less than 10% yields of 3-dimethylamine-1 : 1-diphenylbutyl cyanide (II) on reaction with dimethylamine in ethanol, the major part of the product being either (XII) or its isomer, 1 : 1-diphenylbut-2-enyl cyanide.

Reaction of 2 : 3-dibromopropene (XX) with sodiodiphenylmethyl cyanide gave a bromodiphenylbutenyl cyanide which, in view of the low reactivity of vinyl halides, is assumed to be (XXI) :

$$\underset{\text{(XX.)}}{CH_2{:}CBr{\cdot}CH_2Br} + Ph_2CH{\cdot}CN \xrightarrow{NaNH_2} \underset{\text{(XXI.)}}{CH_2{:}CBr{\cdot}CH_2{\cdot}CPh_2{\cdot}CN}$$

All attempts to reduce (XXI) to 3-bromo-1 : 1-diphenylbutyl cyanide were unsuccessful. Hydrogenation in alcoholic solution in the presence of palladised charcoal removed bromine as fast as it reduced the double bond, and the only product that could be isolated was 1 : 1-diphenylbutyl cyanide; the presence of hydrogen bromide made the hydrogenation slower without affecting the final result. Raney nickel was gradually inactivated by the hydrogen bromide liberated, and again there was no evidence of selective reduction of the double bond. Hydrogenation was very slow when ether, dioxan, or acetone was used as solvent with palladised charcoal as catalyst, though the use of a more active catalyst (Alexander and Cope, *J. Amer. Chem. Soc.*, 1944, **66**, 886) increased the rate of hydrogenation. In no instance, however, was

there any indication of the formation of the required product. Treatment of (XXI) with activated aluminium failed to cause reduction.

The analgesic activities of the compounds tested are listed in the Table. An outline of the methods of testing is given in Part I, and a more detailed pharmacological report will be published elsewhere.

Analgesic Activities.

Compound.	Analgesic activity * (pethidine = 1).
$NMe_2 \cdot CHMe \cdot CH_2 \cdot CPh_2 \cdot COEt$ (amidone)	8
$O<[CH_2]_4>N \cdot CHMe \cdot CH_2 \cdot CPh_2 \cdot COEt$	20
$O<[CH_2]_4>N \cdot CH_2 \cdot CHMe \cdot CPh_2 \cdot COEt$	1—2
$O<[CH_2]_4>N \cdot CH_2 \cdot CHMe \cdot CPh_2 \cdot C(:NH)Et$	1—3

* The relative activities are quoted on a weight basis.

Experimental.

(M. p.s are corrected.)

2-Nitropropan-1-ol.—The method of Vanderbilt and Hass (*Ind. Eng. Chem.*, 1940, **32**, 34) gave a poor yield of 2-nitropropan-1-ol, together with 2-nitro*iso*butane-1 : 3-diol and unchanged nitroethane (cf. Blicke, Faust, Warzynski, and Gearien, *J. Amer. Chem. Soc.*, 1945, **67**, 205). The method of Earl, Ellsworth, Jones, and Kenner (*J.*, 1928, 2697) for the preparation of the sodium salt was found to be satisfactory, their yield being improved by concentration of the methanol mother-liquors from the first crop of sodium salt. The 2-nitropropan-1-ol was obtained by dissolving the sodium salt in a little water and adding ether and then a slight excess of 2N-sulphuric acid with stirring, the temperature being kept below 10°. The ether layer was separated, the aqueous layer was extracted thoroughly with ether, and the combined extracts were dried (Na_2SO_4). After removal of the solvent, 2-nitropropan-1-ol distilled at 100°/12 mm. (Vanderbilt and Hass, *loc. cit.*, give b. p. 99°/10 mm.). The overall yield was 65%.

2-Aminopropan-1-ol.—A solution of 2-nitropropan-1-ol (105 g.) in a mixture of methanol (300 c.c.) and water (30 c.c.) was hydrogenated at room temperature in the presence of Raney nickel (15 g.) (initial pressure, 50 atmospheres). The catalyst was filtered off, the methanol removed, and the residue fractionated under reduced pressure. 2-Aminopropan-1-ol boiled at 76—78°/15 mm. (Blicke, Faust, Warzynski, and Gearien, *loc. cit.*, give b. p. 80—86°/20 mm.). Yield 55·3 g., 74%.

2-Dimethylaminopropan-1-ol.—2-Aminopropan-1-ol (20 g.) was added gradually to a mixture of formic acid (61 g.) and water (7 c.c.) with ice cooling. Aqueous formaldehyde (36%; 49 c.c.) was added, and the mixture was heated on the water-bath for about 20 hours. 10N-Hydrochloric acid (35 c.c.) was added, and the mixture was evaporated under reduced pressure from a steam-bath. The residue was treated with an excess of 40% sodium hydroxide solution with cooling, and was extracted thoroughly with ether. The extract was dried (K_2CO_3), the ether removed, and the residue distilled. 2-Dimethylaminopropan-1-ol boiled at 65°/37 mm. (Karrer *et al.*, *Helv. Chim. Acta*, 1922, **5**, 469, give b.p. 140—141°/738 mm.). Yield 22·6 g., 82%.

1-Chloro-2-dimethylaminopropane.—A solution of 2-dimethylaminopropan-1-ol (22·0 g.) in benzene (250 c.c.) was treated with thionyl chloride (31 c.c.), added gradually with cooling and occasional shaking. When the addition was complete, the mixture was boiled under reflux for 2 hours and was then left overnight in the refrigerator. The white solid was filtered off and dried (32·2 g.). The picrate, prepared directly from the hydrochloride, or from a sample of distilled base (b. p. 124—126°), melted at 158·5—161° after crystallisation from ethanol (Found : N, 15·8; Cl, 10·1. Calc. for $C_5H_{12}NCl,C_6H_3O_7N_3$: N, 16·0; Cl, 10·1%) (Schultz and Sprague, *loc. cit.*, give m. p. 166—167°).

3-Dimethylamino-1 : 1-diphenylbutyl Cyanide.—The above chloro-amine hydrochloride (15 g.) was dissolved in a little water. Excess of potassium carbonate solution was added, and the oil was extracted immediately with benzene (about 150 c.c. in all); the extract was dried (K_2CO_3) and used without delay.

A solution of diphenylmethyl cyanide (18 g.) in dry benzene (125 c.c.) was treated with sodamide (3·75 g.), and the mixture was stirred at room temperature till there was no apparent further reaction. The benzene solution of the chloro-amine was added, and the mixture was stirred overnight at room temperature. The mixture was extracted with three 60 c.c. portions of 2N-hydrochloric acid, the acid extract was basified with 40% sodium hydroxide solution, and the oil was extracted with ether. The extract was dried (K_2CO_3), the ether removed, and the residue distilled. The product (18·4 g., 71% yield) boiled at 128°/0·1 mm. and solidified on standing. Two crystallisations from aqueous alcohol gave colourless needles, m. p. 92—92·5° (Found : C, 82·2; H, 8·1; N, 10·0. Calc. for $C_{19}H_{23}N_3$: C, 82·0; H, 8·0; N, 10·1%) (Schultz, Robb, and Sprague, *J. Amer. Chem. Soc.*, 1947, **69**, 2454, give m. p. 90—91°). Yield of pure product 9·3 g., 36%.

6-Dimethylamino-4 : 4-diphenylheptan-3-one.—A solution of 3-dimethylamino-1 : 1-diphenylbutyl cyanide (11·1 g.) in dry toluene (30 c.c.) was added to a Grignard reagent prepared from magnesium (1·9 g.) and ethyl iodide (12·5 g.) in ether (30 c.c.). The ether was distilled from a water-bath till the temperature of the residue was 95—97°, and the residue was heated overnight on the water-bath. The mixture was decomposed with 2N-hydrochloric acid (200 c.c.), the decomposition being completed by heating on a water-bath for 30 minutes. The toluene layer was removed and extracted with hydrochloric acid. The combined acid solutions, together with a lower gummy layer, were made alkaline with 40% sodium hydroxide solution. The oil was extracted with ether, the extract was dried (K_2CO_3), the ether was removed, and the residue distilled. The ketone (10·3 g.; 83%) boiled at 154—160°/1 mm. The *hydrochloride*, after crystallisation from methyl cyanide, melted at 231—233° (Found : C, 72·8;

H, 8·6; N, 4·2; Cl, 10·1. $C_{21}H_{27}ON,HCl$ requires C, 72·9; H, 8·2; N, 4·05; Cl, 10·25%) (Thorp, Walton, and Ofner, *Nature*, 1947, **159**, 679; 1947, **160**, 605, give m. p. 231° but quote no analytical figures).

Ethyl α-Morpholinopropionate.—Morpholine (88 g.) was added gradually to a solution of ethyl α-bromopropionate (45 g.) in benzene (100 c.c.). The mixture was boiled under reflux for 1 hour, and, after cooling, the precipitate of morpholine hydrobromide was filtered off and washed with benzene. The combined filtrate and washings were extracted with an excess of 5N-hydrochloric acid, and the acid extract was made strongly alkaline with 2N-sodium hydroxide with cooling and extracted thoroughly with ether. The extract was dried (Na_2SO_4), the ether removed, and the residue distilled. *Ethyl α-morpholinopropionate* boiled at 110—113°/15 mm. (Found: C, 57·7; H, 9·2; N, 6·95. $C_9H_{17}O_3N$ requires C, 57·7; H, 9·1; N, 7·5%).

2-*Morpholinopropan*-1-*ol.*—(a) *By reduction of ethyl α-morpholinopropionate.* Sodium (125 g.) was covered with dry toluene in a 3-l. flask equipped with mercury-sealed wire stirrer, dropping funnel, and a long, wide-bore condenser. The toluene was heated to boiling, the flame was removed, and the mixture was stirred rapidly till it had cooled considerably. When the suspension of finely-divided sodium had cooled to room temperature, a solution of ethyl α-morpholinopropionate (81 g.) in dry ethanol (125 c.c.) was added as rapidly as possible, followed by sufficient dry alcohol (also added rapidly) to decompose all the sodium, the mixture being stirred vigorously throughout. The reaction was completed by boiling under reflux for 30 minutes. After cooling, ice was added to decompose the sodium ethoxide, and the solution was distilled in steam until no further basic material passed over. The distillate was acidified to Congo-red with concentrated hydrochloric acid, and was then evaporated under reduced pressure to a syrup; the cooled residue was covered with ether, and made strongly alkaline by the addition of 40% sodium hydroxide. The ether layer was separated, and the aqueous layer was saturated with sodium hydroxide and extracted thoroughly with ether. The combined ether extracts were dried (K_2CO_3), the ether removed, and the residue distilled. 2-Morpholinopropan-1-ol boiled at 121—124°/18 mm. Yield 28·8 g., 46%. The *α-naphthylurethane*, after crystallisation from benzene–petroleum, melted at 102—105° (Found: C, 69·2; H, 7·1; N, 8·85. $C_{18}H_{22}O_3N_2$ requires C, 68·8; H, 7·05; N, 8·9%).

(b) *From* 2-*aminopropan*-1-*ol.* A mixture of di-(2-chloroethyl) ether (38 g.), 2-aminopropan-1-ol (20 g.), and anhydrous potassium carbonate (42 g.) was heated in an oil-bath at 150° for 8 hours. After cooling, ether was added, the mixture was filtered, and the solid was washed thoroughly with ether. The combined filtrate and washings were treated with solid potassium hydroxide, the ether layer was separated, and the aqueous layer extracted with ether. The combined extracts were dried (K_2CO_3), the solvent removed, and the residue distilled. The fraction of b. p. 80—110°/15 mm. was redistilled to give 2-morpholinopropan-1-ol, b.p. 105—107°/12 mm. Yield 23·4 g., 61%.

1-*Chloro*-2-*morpholinopropane.*—2-Morpholinopropan-1-ol (22·7 g.) in dry benzene (230 c.c.) was treated with thionyl chloride (28 c.c.), added gradually with occasional shaking, the solution being cooled in ice. When the addition was complete, the mixture was boiled under reflux for 2 hours, and was then left overnight in the refrigerator; the solid was filtered off, washed thoroughly with dry benzene, and dried. Yield 28 g., 89%.

The hydrochloride could be crystallised from ethyl acetate, but it was extremely deliquescent. The base, obtained in 83% yield, boiled at 88—91°/10 mm. It was used for the next stage without delay.

The *picrate*, prepared in ethanol, melted at 104—107°. After crystallisation from ethanol the m. p. was 105—107° (Found: N, 14·5; Cl, 9·1. $C_7H_{14}ONCl,C_6H_3O_7N_3$ requires N, 14·3; Cl, 9·0%).

Reaction of 1-*Chloro*-2-*morpholinopropane with Diphenylmethyl Cyanide.*—A solution of diphenylmethyl cyanide (9·7 g.) in dry benzene (75 c.c.) was treated with sodamide (2·0 g.), and the mixture was stirred at room temperature for about 2 hours. A solution of 1-chloro-2-morpholinopropane (8·2 g.) in dry benzene (75 c.c.) was added, and the mixture was stirred overnight at room temperature. The mixture was extracted with excess of 2N-hydrochloric acid, the extract was made strongly alkaline with 40% sodium hydroxide, and the oil was extracted with ether. Removal of the ether, and crystallisation of the residue from petroleum gave a solid which melted between 94° and 124°. Yield 8·05 g., 50% Crystallisation of the solid from benzene–petroleum (b. p. 60—80°) gave two types of crystals: clusters of small plates (*A*), and cubes (*B*). These were separated by hand, and each of the solids was crystallised from petroleum (b. p. 80—100°). Compound (*A*) melted at 140—141° alone or mixed with an authentic specimen of 1 : 1-*diphenyl*-3-*morpholinoisobutyl cyanide* (see below) (Found: C, 78·9; H, 7·6; N, 9·1. $C_{21}H_{24}ON_2$ requires C, 78·7; H, 7·55; N, 8·7%). Compound (*B*) melted at 107—108° alone or mixed with an authentic specimen of 1 : 1-*diphenyl*-3-*morpholinobutyl cyanide* (Found: C, 78·5; H, 7·5; N, 9·3%).

Comparison of the melting range of the crude product with those of synthetic mixtures of the pure cyanides indicated that it contained approximately 60% of (*B*).

No simple method could be found for separating the isomers in good yield, but pure specimens of 1 : 1-diphenyl-3-morpholinobutyl cyanide could be obtained by crystallisation of the mixture from ether, and of 1 : 1-diphenyl-3-morpholino*iso*butyl cyanide by crystallisation from acetone. In both cases the recovery was poor.

1-*Morpholinopropan*-2-*ol.*—Morpholine (43·5 g.), propylene oxide (30 g.), and methanol (10 c.c.) were boiled under reflux for 2 hours. Distillation under reduced pressure gave 1-morpholinopropan-2-ol as a colourless oil, b. p. 94—96°/17 mm. (Found: C, 57·85; H, 10·2; N, 10·1. Calc. for $C_7H_{15}O_2N$: C, 57·9; H, 10·4; N, 9·65%) (Cheney and Bywater, *J. Amer. Chem. Soc.*, 1942, **64**, 970, give b. p. 82—84°/1·5 mm.). Yield 63·5 g., 88%.

An attempt to prepare an α-naphthylurethane by warming with α-naphthyl *iso*cyanate was unsuccessful.

2-*Chloro*-1-*morpholinopropane.*—The hydrochloride was prepared from 1-morpholinopropan-2-ol (35 g.), benzene (250 c.c.), and thionyl chloride (60 c.c.) by the method used for the preparation of 1-chloro-2-morpholinopropane hydrochloride. The *hydrochloride*, which was obtained in 89% yield, melted at 176—178° after crystallisation from ethyl acetate–ethanol (Found: C, 42·4; H, 7·5. $C_7H_{14}ONCl,HCl$ requires C, 42·0; H, 7·6%). The base, obtained from the hydrochloride in 86% yield,

boiled at 82·5—83°/12 mm. The *picrate* separated from ethanol in yellow crystals, m. p. 117—119°, unchanged on crystallisation from the same solvent (Found: N, 14·4; Cl, 8·75. $C_7H_{14}ONCl,C_6H_3O_7N_3$ requires N, 14·3; Cl, 9·0%).

Reaction of 2-Chloro-1-morpholinopropane with Diphenylmethyl Cyanide.—The reaction was carried out by precisely the same method as was used for the isomeric 1-chloro-2-morpholinopropane, the mixture of cyanides being obtained in 80% yield. The mixture again contained some 60% of 1 : 1-diphenyl-3-morpholinobutyl cyanide.

On one occasion the two cyanides were separated during their extraction from benzene solution with 2N-hydrochloric acid. The hydrochloride of 1 : 1-diphenyl-3-morpholino*iso*butyl cyanide solidified, while that of 1 : 1-diphenyl-3-morpholinobutyl cyanide remained liquid. The two hydrochlorides were separated by filtration, and converted into the bases. Attempts to repeat this separation were always unsuccessful, both hydrochlorides solidifying simultaneously.

*Unambiguous Synthesis of 1 : 1-Diphenyl-3-morpholino*isobutyl *Cyanide.*—*3-Chloro-1 : 1-diphenyl-*isobutyl *cyanide.* A solution of diphenylmethyl cyanide (19·3 g.) in benzene (150 c.c.) was treated with sodamide (4·0 g.), and the mixture was boiled under reflux with stirring until the separation of the solid was complete. The suspension was cooled to room temperature and 1-chloro-2-bromopropane (Dewael, *Bull. Soc. chim. Belg.*, 1930, **39**, 87) (15·75 g.) was added slowly. The mixture was boiled under reflux with stirring for 2 hours, and after cooling was washed successively with 2N-hydrochloric acid and water, and was dried (Na_2SO_4). The benzene was removed and the residue distilled. The material boiling at 118—120°/0·2 mm. was redistilled giving *3-chloro-1 : 1-diphenyl*isobutyl *cyanide*, b.p. 110°/0·001 mm. (Found: N, 5·0; Cl, 13·1. $C_{17}H_{16}NCl$ requires N, 5·2; Cl, 13·1%). Yield 18·9 g., 70%.

*1 : 1-Diphenyl-3-morpholino*isobutyl *cyanide.* 3-Chloro-1 : 1-diphenyl*iso*butyl cyanide (2·05 g.) and morpholine (10 c.c.) were heated at 150° in a sealed tube for 6 hours. After cooling, ether was added, and morpholine hydrochloride was filtered off. The filtrate was extracted with an excess of 2N-hydrochloric acid and the extract was made strongly alkaline with 40% sodium hydroxide and extracted with ether. The extract was dried (Na_2SO_4) and evaporated, leaving a syrupy residue to which petrol (b. p. 80—100°) was added. The crystalline solid was filtered off, and recrystallised from benzene–petroleum (b. p. 40—60°), and then melted at 139—140°. Yield 0·43 g., 18%.

Unambiguous Synthesis of 1 : 1-Diphenyl-3-morpholinobutyl Cyanide.—*1 : 1-Diphenylbut-3-enyl cyanide.* Diphenylmethyl cyanide (193 g.) in benzene (1500 c.c.) was treated with sodamide (41 g.), and the mixture was boiled under reflux and stirred until the separation of solid was complete. After cooling, allyl chloride (80·5 g.) was added gradually, and the mixture was then boiled under reflux with stirring for 2 hours. The cooled solution was washed with 2N-hydrochloric acid, then with water, and was dried (Na_2SO_4). The benzene was removed and the residue distilled, giving the cyanide, b. p. 125°/0·2 mm. The material solidified and then melted at 24·5°, but it could not be recrystallised (Found: C, 87·7; H, 6·3; N, 6·0. Calc. for $C_{17}H_{15}N$: C, 87·5; H, 6·5; N, 6·0%) (Schultz, Robb, and Sprague, *loc. cit.*, give b. p. 131°/1·5 mm.). Yield 219 g., 94%. Allyl bromide could be used in place of allyl chloride with very similar results.

1 : 1-Diphenyl-3-morpholinobutyl cyanide. 1 : 1-Diphenylbut-3-enyl cyanide (5 g.), a solution of hydrogen bromide in acetic acid (50%; 20 c.c.), and diphenylamine (0·2 g.) were placed in a nitrogen-filled Carius tube, and heated overnight at 120°. After cooling, the contents of the tube were diluted with water, and the oil was extracted with ether. The extract was washed first with water, then with sodium hydrogen carbonate solution till free from acid, and then again with water. It was dried ($CaCl_2$), and the ether removed leaving a reddish oil (3·3 g.). Morpholine (2·1 c.c.) was added, and the mixture was heated overnight on the water-bath. Dry ether was added, the solid filtered off, and the filtrate extracted with three 20 c.c. portions of 2N-hydrochloric acid. The acid extract was made strongly alkaline with 40% sodium hydroxide, and extracted with ether. The extract was dried (K_2CO_3), and the solvent removed. The residual oil (0·45 g.) was dissolved in hot petroleum (b. p. 80—100°). On standing, a solid (*A*) separated, and was filtered off; the filtrate, on concentration, yielded a second crystalline substance (*B*). The solid (*A*) (0·08 g.) melted at 135·5—137·5° after crystallisation from benzene–petroleum (Found: C, 74·75; H, 7·85; N, 8·0%). The structure of this compound is not known. Substance (*B*) (0·17 g.) melted at 105—107°, the melting point not being depressed on admixture with the material, m. p. 107—108°, obtained as described above.

The same result was obtained in the absence of diphenylamine. The addition of hydrogen bromide was attempted in a number of different solvents and under a wide range of conditions, but no appreciable increase in yield resulted.

4 : 4-Diphenyl-6-morpholinoheptan-3-one.—A solution of 1 : 1-diphenyl-3-morpholinobutyl cyanide (12·9 g.) in dry toluene (32 c.c.) was added to a Grignard reagent prepared from magnesium (1·98 g.), ethyl iodide (12·6 g.), and ether (30 c.c.). The ether was distilled off from a water-bath until the internal temperature reached 97°, and the residue was heated overnight on the water-bath. The reaction mixture was decomposed with 2N-hydrochloric acid (200 c.c.), the decomposition being completed by warming on the water-bath for 30 minutes. The toluene layer was separated and washed twice with small quantities of 2N-hydrochloric acid. The combined acid solutions, containing a heavy oily layer, were made strongly alkaline with 40% sodium hydroxide solution, and extracted with benzene. The extract was dried (K_2CO_3) and the solvent removed, leaving a yellow oil (13·9 g.). A solution of this oil in dry ether was treated with dry hydrogen chloride, and the precipitated salt was crystallised from methyl cyanide. *4 : 4-Diphenyl-6-morpholinoheptan-3-one hydrochloride* melted at 224—229° (Found: C, 70·8; H, 7·7; N, 3·6; Cl, 9·2. $C_{23}H_{29}O_2N,HCl$ requires C, 71·2; H, 7·8; N, 3·6; Cl, 9·1%). Yield 11·4 g., 73%.

The *base*, liberated from the pure hydrochloride, melted at 75·5—77° after crystallisation from aqueous ethanol (Found: C, 78·5; H, 8·0; N, 4·4. $C_{23}H_{29}O_2N$ requires C, 78·6; H, 8·3; N, 4·0%).

The *hydrobromide*, after crystallisation from water containing a trace of hydrobromic acid, melted at 235—237° (Found: N, 3·4; Br, 18·9. $C_{23}H_{29}O_2N,HBr$ requires N, 3·2; Br, 18·5%). The *nitrate* melted at 175° after crystallisation from ethanol–ether (Found: C, 66·7; H, 7·25; N, 6·6. $C_{23}H_{29}O_2N,HNO_3$ requires C, 66·6; H, 7·3; N, 6·8%). The *oxalate* had m. p. 162—163° after crystallis-

ation from ethanol–ether (Found: C, 68·3; H, 7·0; N, 3·3. $C_{23}H_{29}O_2N,C_2H_2O_4$ requires C, 68·0; H, 7·1; N, 3·2%).

4 : 4-*Diphenyl*-6-*morpholino*-5-*methylhexan*-3-*one*.—A solution of 1 : 1-diphenyl-3-morpholino*iso*-butyl cyanide (3·2 g.) in toluene (15 c.c.) was added to a Grignard reagent prepared from magnesium (0·5 g.) and ethyl iodide (3·2 g.) in ether. Ether was removed by distillation until the internal temperature reached 97°, and the residue was heated overnight on the water-bath. The Grignard complex was decomposed with an excess of 2N-hydrochloric acid, and the resulting mixture was treated with ammonium chloride and ammonia. The oil was extracted with benzene, the extract dried (K_2CO_3), and the solvent removed, leaving an oil (3·36 g.) from which 3-*imino*-4 : 4-*diphenyl*-6-*morpholino*-5-*methylhexane* was obtained by crystallisation from petroleum; the compound melted at 103—106° (Found: C, 79·2; H, 9·0; N, 7·8. $C_{23}H_{30}ON_2$ requires C, 78·8; H, 8·6; N, 8·0%). The *dihydrochloride*, containing alcohol of crystallisation, melted at 200—203° after crystallisation from this solvent (Found: C, 64·2; H, 8·1; N, 5·9; Cl, 15·5. $C_{23}H_{30}ON_2,2HCl,C_2H_6O$ requires C, 63·95; H, 8·2; N, 6·0; Cl, 15·1%).

The imine (2 g.) was boiled under reflux overnight with concentrated hydrochloric acid (10 c.c.). The cooled solution was made strongly alkaline with sodium hydroxide, and extracted with benzene. Evaporation of the dry benzene extract left an oil which soon solidified. 4 : 4-*Diphenyl*-6-*morpholino*-5-*methylhexan*-3-*one* melted at 130—130·5° after crystallisation from ethanol (Found: C, 78·65; H, 8·5; N, 4·2. $C_{23}H_{29}O_2N$ requires C, 78·6; H, 8·3; N, 4·0%). The *hydrochloride* melted at 218—222° after crystallisation from acetone–ether and drying at 100° (Found: C, 71·1; H, 7·65; N, 3·3; Cl, 8·6. $C_{23}H_{29}O_2N,HCl$ requires C, 71·2; H, 7·8; N, 3·6; Cl, 9·1%).

αα-Diphenyl-γ-butyrolactone.—Diphenylmethyl cyanide (9·6 g.) in dry benzene (75 c.c.) was treated with sodamide (2 g.), and the mixture was boiled under reflux and stirred till no more solid separated. The mixture was cooled in ice and stirred while ethylene oxide (2·2 g.) was passed in; the suspended solid largely went into solution during this process. The mixture was stirred overnight at room temperature, and was then extracted with 2N-hydrochloric acid. The acid washings slowly deposited the *lactone* (6·8 g.; 57%) which melted at 80—80·5° after crystallisation from petroleum (b. p. 60—80°) (Found: C, 80·7; H, 6·1. $C_{16}H_{14}O_2$ requires C, 80·7; H, 5·9%).

When sodium ethoxide replaced sodamide in the above experiment the same product was obtained in 46% yield; refluxing the solution for three hours after the addition of ethylene oxide increased the yield to 52%. When reaction was carried out in alcohol with sodium ethoxide as condensing agent, the diphenylmethyl cyanide was largely recovered unchanged, the only other pure product isolated being diphenylacetamide.

αα-Diphenyl-γ-valerolactone.—(a) *From diphenylmethyl cyanide and propylene oxide*. Diphenylmethyl cyanide (9·6 g.) was converted into its sodio-derivative by treatment with sodamide (2 g.) in boiling benzene (75 c.c.). A solution of propylene oxide (3·6 c.c.) in dry benzene (15 c.c.) was added gradually to the stirred, ice-cooled suspension. When the addition was complete, the mixture was stirred for 30 minutes at 0° and for three hours at room temperature. The mixture was extracted with an excess of 2N-hydrochloric acid. On standing, the extract deposited an oil which solidified. After several days, the solid (8·7 g.; 69% yield) was filtered off and crystallised from benzene–petroleum (b. p. 60—80°). The lactone melted at 115—116° alone or mixed with a specimen obtained as described below (Found: C, 80·8; H, 6·5. Calc. for $C_{17}H_{16}O_2$: C, 80·9; H, 6·4%).

In one experiment, crystallisation of the crude lactone yielded some benzene-insoluble material which melted at 221° after crystallisation from ethanol–ether, and which was rapidly hydrolysed to αα-diphenyl-γ-valerolactone by means of warm 2N-hydrochloric acid. The analysis indicates that the substance is 2-imino-3 : 3-diphenyl-5-methyltetrahydrofuran hydrochloride (Found: N, 5·1; Cl, 12·5. Calc. for $C_{17}H_{17}ON,HCl$: N, 4·9; Cl, 12·3%) (Easton, Gardner, and Stevens, *loc. cit.*, p. 2941, give m. p. 112—113° for the lactone and m. p. 220—222° for the imine hydrochloride).

(b) *From* 1 : 1-*diphenylbut*-3-*enyl cyanide*. A solution of the cyanide (4·9 g.) in 50% hydrogen bromide in acetic acid (20 c.c.) was heated at 120° for 48 hours in a Carius tube. The contents of the tube, which were largely crystalline, were dissolved in benzene and the solution was washed first with water, then with sodium hydrogen carbonate solution; the solution was then dried (Na_2SO_4) and evaporated to dryness. On trituration with ether the lactone was obtained, melting at 113—115°. Yield 3·5 g., 66%.

Reaction of 1 : 1-*Diphenylbut*-3-*enyl Cyanide with Hydrogen Iodide and Conversion of the Product into* 1 : 1-*Diphenyl*-3-*morpholinobutyl Cyanide*.—1 : 1-Diphenylbut-3-enyl cyanide (10·9 g.) was saturated with hydrogen iodide; the solution was cooled to −80° in a Carius tube, and hydrogen iodide (6 c.c.) was condensed into the solution. The tube was sealed and heated at 80° for 18 hours. The contents of the tube were diluted with water and extracted with ether. The extract was washed successively with water, sodium hydrogen carbonate solution, and sodium sulphite solution, and was then dried ($CaCl_2$). The solvent was removed, and to the residue were added morpholine (8 c.c.) and xylene (40 c.c.). The mixture was heated on the water-bath for three hours, and the basic material was isolated. 1 : 1-Diphenyl-3-morpholinobutyl cyanide (2·8 g.; 19% yield) was obtained, melting at 107—108° after crystallisation from petroleum.

Variation of these conditions invariably resulted in a lower yield of product; neither ascaridole nor benzoyl peroxide had any effect on the yield. The use of ether as solvent was equally unsuccessful.

3 : 4-*Dichloro*-1 : 1-*diphenylbutyl Cyanide*.—1 : 1-Diphenylbut-3-enyl cyanide (23·3 g.) was dissolved in chloroform and an excess of chlorine was passed in, the temperature being kept below 20°. The chloroform solution was washed with 10% sodium sulphite solution, dried (Na_2SO_4), and evaporated to dryness, leaving a gummy residue (29·5 g.) of the *dichloro*-compound which could not be made to crystallise (Found: Cl, 21·1. $C_{17}H_{15}NCl_2$ requires Cl, 23·3%). A portion of the product was distilled, and had b.p. 138°/0·0005 mm.; the chlorine value was still low (Found: N, 4·5; Cl, 20·8. $C_{17}H_{15}NCl_2$ requires N, 4·6; Cl, 23·3%).

Reaction of 3 : 4-*Dichloro*-1 : 1-*diphenylbutyl Cyanide with Morpholine*.—The cyanide (3·04 g.) was boiled under reflux with morpholine (10 c.c.) for 2 hours and, after cooling, ether was added, and

morpholine hydrochloride was filtered off. The filtrate was extracted with 2N-hydrochloric acid, and the extract was basified with sodium hydroxide solution, and extracted with ether. The extract was dried (Na_2SO_4) and evaporated to dryness. Trituration of the residue with ether, and addition of petroleum (b. p. 40—60°) yielded 1 : 1-*diphenyl*-3 : 4-*dimorpholinobutyl cyanide*, m. p. 133° after crystallisation from petroleum (b. p. 100—120°) (Found: C, 74·4; H, 7·6; N, 10·4. $C_{25}H_{31}O_2N_3$ requires C, 74·0; H, 7·7; N, 10·4%). Yield 3·2 g.

When the dichloro-compound (3·04 g.) was refluxed with morpholine (1·74 c.c.) and xylene (15 c.c.) the only basic product isolated was the same dimorpholino-compound.

3 : 4-*Dibromo*-1 : 1-*diphenylbutyl Cyanide*.—1 : 1-Diphenylbut-3-enyl cyanide (23·3 g.) in chloroform (100 c.c.) was treated with a solution of bromine (16 g.) in chloroform (50 c.c.), the temperature being kept below 20°. The solution was washed with 10% sodium sulphite solution and dried ($MgSO_4$). Evaporation to dryness followed by trituration with ether and addition of petroleum yielded 3 : 4-*dibromo*-1 : 1-*diphenylbutyl cyanide*, m. p. 71° after crystallisation from benzene–petroleum (b. p. 40—60°) (Found: C, 52·6; H, 4·1; N, 3·6; Br, 40·3. $C_{17}H_{15}NBr_2$ requires C, 51·9; H, 3·85; N, 3·6; Br, 40·7%). Yield 28·6 g., 73%.

Reaction of 3 : 4-*Dibromo*-1 : 1-*diphenylbutyl Cyanide with Morpholine*.—The cyanide (7·25 g.) was boiled under reflux with morpholine (25 c.c.) for 2 hours. Ether was added to the cold solution, morpholine hydrobromide was filtered off, and the basic material was isolated from the filtrate. 1 : 1-Diphenyl-3 : 4-dimorpholinobutyl cyanide (5·3 g.; 71% yield) was obtained, m. p. 131°, undepressed on admixture with a specimen prepared as described above.

When the amount of morpholine was reduced to 2 mols. the only basic material isolated was the same dimorpholino-compound.

3-*Chloro*-1 : 1-*diphenylbutyl Cyanide*.—Diphenylmethyl cyanide (9·7 g.) was converted into its sodio-derivative by treatment with sodamide (2·0 g.) in boiling benzene (75 c.c.). The suspension was cooled while 2-chloro-1-bromopropane (Kharasch, Engelmann, and Mayo, *J. Org. Chem.*, 1937, **2**, 288) (7·9 g.) was added, and the mixture was boiled under reflux for 2 hours. After cooling, the solution was washed successively with 2N-hydrochloric acid and sodium hydrogen carbonate solution, and was dried ($CaCl_2$). After the benzene had been removed the residue was distilled, and the fraction, b. p. 115—120°/0·0003 mm., was collected. On crystallisation from petroleum (b. p. 40—60°) the compound melted at 59° (Found: C, 75·9; H, 5·95; N, 5·1; Cl, 12·7. Calc. for $C_{17}H_{16}NCl$: C, 75·7; H, 6·0; N, 5·2; Cl, 13·1%). Yield 6·4 g., 47% (Easton, Gardner, and Stevens, *loc. cit.*, p. 2941, give m. p. 53—55°).

1 : 1-*Diphenyl*-3-*morpholinobutyl Cyanide*.—3-Chloro-1 : 1-diphenylbutyl cyanide (2·0 g.) and morpholine (10 c.c.) were heated at 150° in a sealed tube for 6 hours. The mixture was worked up to yield 1 : 1-diphenyl-3-morpholinobutyl cyanide (0·5 g.; 21% yield), m. p. 105—107° after crystallisation from petroleum (b. p. 60—80°).

3-*Bromo*-1 : 1-*diphenylbut*-3-*enyl Cyanide*.—Diphenylmethyl cyanide (38·6 g.) was converted into its sodio-derivative by treatment with sodamide (8 g.) in boiling benzene (300 c.c.). 2 : 3-Dibromopropene (Lespieau and Bourguel, *Org. Synth.*, Coll. Vol. I, p. 203) (40 g.) was added slowly to the cooled suspension. The mixture was boiled under reflux for 2 hours with stirring. The cooled mixture was washed with 2N-hydrochloric acid and then with water, and was dried (Na_2SO_4). The benzene was removed, and the residue distilled; the distillate crystallised on standing, and the *cyanide* melted at 54—55° after crystallisation from benzene–petroleum (b. p. 40—60°) (Found: C, 65·4; H, 4·6; N, 4·7; Br, 25·3. $C_{17}H_{14}NBr$ requires C, 65·4; H, 4·5; N, 4·5; Br, 25·6%). Yield 44 g., 71%.

Hydrogenation of 3-*Bromo*-1 : 1-*diphenylbut*-3-*enyl Cyanide*.—Hydrogenation in ethanol solution in the presence of 10% palladised charcoal led to the absorption of 2 mols. of hydrogen without a break and to the formation of 1 : 1-diphenylbutyl cyanide; this compound boiled at 85°/0·01 mm. (Found: C, 87·1; H, 7·1; N, 6·1. Calc. for $C_{17}H_{17}N$: C, 86·8; H, 7·3; N, 5·95%) (Schultz, Robb, and Sprague, *loc. cit.*, give b. p. 125—127°/1 mm.).

Interruption of the hydrogenation at various stages, and titration of the hydrogen bromide liberated showed that for every g.-mol. of hydrogen absorbed roughly 0·5 g.-mol. of hydrogen bromide was formed, and hence that the bromine was being removed as rapidly as the double bond was being reduced.

The authors wish to express their thanks to Miss M. A. Smith and to Mr. G. B. Webb for assistance in the experimental work.

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[*Received, May 14th*, 1948.]

NOTES.

The Thermal Decomposition of Phenacyltrimethylammonium Hydroxide. By J. HARLEY-MASON.

IT was observed by Stevens *et al.* (*J.*, 1928, 3193) that phenacylbenzyldimethylammonium hydroxide rearranges in alkaline solution with migration of the benzyl group. Under the same conditions phenacyltrimethylammonium hydroxide (I) does not rearrange. In an attempt to determine whether a methyl group was capable of migration under more drastic conditions, (I) was submitted to thermal decomposition at 200°. The products were trimethylamine, water, and *cis*-1 : 2 : 3-tribenzoyl*cyclo*propane, identical with the product obtained by Paal and Schulze (*Ber.*, 1903, **36**, 2425) by the action of sodium on phenacyl iodide, together with a small amount of an intensely red substance not identified. No products of rearrangement could be isolated. The decomposition is thus parallel to the thermal

decomposition of diazoacetophenone (Grundmann, *Annalen*, 1938, **536**, 29), and the product presumably arises from the trimerisation of the radical Ph·CO·CH< :

$$Ph\cdot CO\cdot CH_2\cdot NMe_3]OH \xrightarrow[-NMe_3]{-H_2O} Ph\cdot CO\cdot CH< \longrightarrow Ph\cdot CO\cdot CH\begin{matrix}CH\cdot COPh\\ CH\cdot COPh\end{matrix}$$

To a solution of phenacyltrimethylammonium chloride (15 g.) in water (30 c.c.), silver oxide (15 g.) was added with vigorous shaking. After 10 minutes the mixture was filtered and the residue washed with water. The chloride-free filtrate and washings were concentrated in a vacuum to a thick syrup of the quaternary hydroxide, and this was then slowly heated in an oil-bath. When the temperature reached 180° a vigorous decomposition commenced and trimethylamine and steam were evolved. The reaction subsided after 5 minutes and the temperature was then raised to 200° for a further 5 minutes. The deep red melt was allowed to cool somewhat, ethanol (50 c.c.) was added, and the mixture was refluxed for 1 hour. After cooling, the product, which consisted of colourless crystals contaminated with a small amount of an intensely red substance, was collected. Three recrystallisations from glacial acetic acid removed the red material, which remained in the mother liquors, and gave 3·9 g. of colourless needles, m. p. 217°, undepressed by admixture with a sample of *cis*-1 : 2 : 3-tribenzoyl*cyclo*propane prepared by the method of Paal and Schulze (*loc. cit.*).—University Chemical Laboratory, Cambridge. [*Received, May 12th*, 1948.]

A Comparative Study of the Würtz–Fittig and the Clemmensen Method for the Preparation of Aromatic Hydrocarbons. By Hussein A. Fahim and Ahmed Mustafa.

The aim of the present investigation is to study how far the Würtz–Fittig and the Clemmensen method may be applied satisfactorily to the preparation of *n*-alkylbenzenes.

Eisenlohr and Schulz (*Ber.*, 1924, **57**, 1808), Schmidt, Hopp, and Schoeller (*Ber.*, 1939, **72**, 1893), and Shen and Wood (*J. Inst. Petroleum*, 1940, **26**, 514) reported that, in general, the Clemmensen method proved to be unsatisfactory for the preparation of *n*-alkylbenzenes. Consequently, this method has been carefully tested by the synthesis of different *n*-alkylbenzenes and high yields have been obtained (Table I). It should be added, too, that the use of pure as well as commercial zinc granules, in the Clemmensen method did not alter the result.

Table I.

n-Alkylbenzene.	Clemmensen method, % yield.	Würtz–Fittig method, % yield.	*n*-Alkylbenzene.	Clemmensen method, % yield.	Würtz–Fittig method, % yield.
Propylbenzene	82	55	Heptylbenzene	90	70
Butylbenzene	88	70	Octylbenzene	91	40
Amylbenzene	90	55	Nonylbenzene	92	—
Hexylbenzene	91	62			

It seems that in the Würtz–Fittig method the yield of *n*-alkylbenzenes is influenced particularly by the nature of the halogen present in the reacting molecules. The highest yield of hydrocarbon is always obtained when the alkyl and aryl bromides are used, whereas the yield is much less from either alkyl and aryl iodides, or alkyl and aryl chlorides. Furthermore, the amount of the hydrocarbon obtained by the action of bromobenzene and alkyl halide, butyl chloride, bromide, and iodide, invariably follows the sequence: Br > I > Cl. This order is also observed in the synthesis of higher hydrocarbons, *e.g.*, *n*-heptylbenzene. The results obtained are given in Table II.

Table II.

Temp.	Solvent.	Aryl halide.	Alkyl halide.	% Yield (based on aryl halide used).
		n-*Propylbenzene.*		
20°	Ether	Chlorobenzene	*n*-Propyl chloride	7
20	Ether	Iodobenzene	*n*-Propyl iodide	8
20	Ether	Bromobenzene	*n*-Propyl chloride	20
25	Benzene	Bromobenzene	*n*-Propyl iodide	30
20	Ether	Chlorobenzene	*n*-Propyl bromide	32
20	Ether	Bromobenzene	*n*-Propyl bromide	50—55
		n-*Butylbenzene.*		
30—35	Ether	Iodobenzene	*n*-Butyl iodide	7
25	Ether	Chlorobenzene	*n*-Butyl chloride	10
30—40	Benzene	Bromobenzene	*n*-Butyl chloride	20
30—40	Benzene	Chlorobenzene	*n*-Butyl bromide	25
30—40	Benzene	Bromobenzene	*n*-Butyl iodide	40
25	Ether	Bromobenzene	*n*-Butyl bromide	70
30—40	Benzene	Bromobenzene	*n*-Butyl bromide	62—70
		n-*Amylbenzene.*		
30	Ether	Chlorobenzene	*n*-Amyl chloride	5
30	Ether	Iodobenzene	*n*-Amyl iodide	6
30—40	Benzene	Bromobenzene	*n*-Amyl chloride	15
30—40	Benzene	Chlorobenzene	*n*-Amyl bromide	42
30—40	Benzene	Bromobenzene	*n*-Amyl iodide	46
30—40	Benzene	Bromobenzene	*n*-Amyl bromide	50—55

These results lead to the conclusion that the Clemmensen method is more favourable than the Würtz–Fittig method for the preparation of *n*-alkylbenzenes. The latter method, however, may give satisfactory results when the interaction takes place between alkyl and aryl bromides.

Experimental.—The Würtz–Fittig reaction was carried out in a three-necked flask containing the reactants, aryl halide (1 mol.), alkyl halide (1·1 mols.), and finely powdered sodium metal (2·5 atoms), in the presence of a solvent. The mixture was left for 48 hours at room temperature and then fractionated. The benzene solution of the products, prepared from aryl and alkyl chlorides, acquired a greenish fluoresence.

For the preparation of *n*-alkylbenzenes by the Clemmensen method, the corresponding phenyl alkyl ketones were prepared by Friedel–Crafts method in very satisfactory yields. The acid chloride in each case was prepared in almost quantitative yield by refluxing the corresponding acid with excess of thionyl chloride for 24 hours.

The following new derivatives of the ketones have been prepared :

Phenyl n-*butyl ketone* p-*nitrophenylhydrazone*, orange crystals from ethyl alcohol, m. p. 121—122° (Found : C, 68·2; H, 6·7; N, 14·1. $C_{17}H_{19}O_2N_3$ requires C, 68·7; H, 6·4; N, 14·1%); 2 : 4-*dinitrophenylhydrazone*, orange-red crystals from ethyl alcohol, m. p. 123—124° (Found : C, 59·2; H, 5·5; N, 16·4. $C_{17}H_{18}O_4N_4$ requires C, 59·6; H, 5·3; N, 16·4%).

Phenyl n-*amyl ketone* p-*nitrophenylhydrazone*, orange crystals from ethyl alcohol, m. p. 102° (Found : C, 69·3; H, 6·5; N, 13·4. $C_{18}H_{21}O_2N_3$ requires C, 69·4; H, 6·8; N, 13·5%); 2 : 4-*dinitrophenylhydrazone*, orange-red crystals from ethyl alcohol, m. p. 129° (Found : C, 60·6; H, 5·4; N, 15·4. $C_{18}H_{20}O_4N_4$ requires C, 60·7; H, 5·6; N, 15·7%).

Phenyl n-*hexyl ketone* 2 : 4-*dinitrophenylhydrazone*, orange-red crystals from ethyl alcohol, m. p. 131° (Found : C, 61·2; H, 5·7; N, 15·4. $C_{19}H_{22}O_4N_4$ requires C, 61·6; H, 5·9; N, 15·1%).

Phenyl n-*heptyl ketone* p-*nitrophenylhydrazone*, orange crystals from ethyl alcohol, m. p. 113—114° (Found : C, 70·7; H, 7·2; N, 12·0. $C_{20}H_{25}O_2N_3$ requires C, 70·8; H, 7·4; N, 12·4%); 2 : 4-*dinitrophenylhydrazone*, orange-red crystals from ethyl alcohol, m. p. 122° (Found : C, 62·6; H, 6·3; N, 14·3. $C_{20}H_{24}O_4N_4$ requires C, 62·5; H, 6·2; N, 14·6%).

Phenyl n-*octyl ketone* p-*nitrophenylhydrazone*, orange crystals from ethyl alcohol, m. p. 100° (Found : C, 71·3; H, 7·6; N, 12·0. $C_{21}H_{27}O_2N_3$ requires C, 71·3; H, 7·6; N, 11·9%); 2 : 4-*dinitrophenylhydrazone*, orange-red crystals from ethyl alcohol, m. p. 121—122° (Found : C, 63·1; H, 6·7; N, 13·9. $C_{21}H_{26}O_4N_4$ requires C, 63·3; H, 6·5; N, 14·1%).—FOUAD I UNIVERSITY, FACULTY OF SCIENCE, ABBASSIA, CAIRO, EGYPT. [*Received, May 10th*, 1948.]

Some pp′-*Dialkylbenzophenones, and Derivatives of* p-*Alkylbenzoic Acids.* By HUSSEIN A. FAHIM.

BOTH *pp′*-dialkylbenzophenones and *p*-alkylbenzoic acids have been prepared by the Friedel–Crafts condensation of benzene homologues with oxalyl chloride.

pp′-*Dimethylbenzophenone* (Limpricht, *Annalen*, 1900, **312**, 91). A mixture of toluene (10 g., 1·3 mols.), oxalyl chloride (12·5 g., 1 mol.), and carbon disulphide (30 c.c.) was gradually treated with aluminium chloride (21 g., 1·6 mol.) at room temperature, with stirring. The mixture was left overnight, carbon disulphide was removed, and the residue decomposed with ice-cold water. The mass was extracted with ether, and the ethereal solution was shaken repeatedly with dilute alkali. The combined alkali extracts gave, on acidification, *p*-toluic acid (m. p. 180°) in 33% yield. The ether solution, on evaporation of the solvent, furnished *pp′*-dimethylbenzophenone (m. p. 95°) in 55% yield. The p-*nitrophenylhydrazone* crystallised from alcohol in golden yellow crystals, m. p. 153° (Found : C, 73·0; H, 5·5; N, 11·9. $C_{21}H_{19}O_2N_3$ requires C, 73·0; H, 5·5; N, 12·2%), and the *semicarbazone* from benzene–light petroleum in white prisms, m. p. 140° (Found : C, 71·7; H, 6·3; N, 16·1. $C_{16}H_{17}ON_3$ requires C, 71·9; H, 6·4; N, 15·7%).

pp′-*Diethylbenzophenone* (Koslow, Fedossejew, and Olifsson, *J. Gen. Chem. Russia*, 1936, **6**, 259). A mixture of ethylbenzene (14 g., 1·3 mols.), oxalyl chloride (12·5 g., 1 mol.), and carbon disulphide (30 c.c.) was gradually treated with aluminium chloride (21 g., 1·5 mols.). The yields of *p*-ethylbenzoic acid (m. p. 112—113°) and *pp′*-diethylbenzophenone were 30 and 45% respectively. Schönberg and Kraemer (*Ber.*, 1922, **55**, 1174) isolated *p*-ethylbenzoic acid as the sole product. The ketone, which solidified when kept in the cold for some days, crystallised from alcohol in white needles, m. p. 47° (Found : C, 85·6; H, 7·5. Calc. for $C_{17}H_{18}O$: C, 85·7; H, 7·5%). The p-*nitrophenylhydrazone* crystallised from alcohol in orange needles, m. p. 99—100° (Found : C, 73·8; H, 6·2; N, 10·8. $C_{23}H_{23}O_2N_3$ requires C, 73·9; H, 6·2; N, 11·3%).

pp′-*Di*-n-*propylbenzophenone*. A mixture of *n*-propylbenzene (24 g., 2 mols.), oxalyl chloride (12·5 g., 1 mol.), and carbon disulphide (30 c.c.) was gradually treated with aluminium chloride (33·5 g., 2·5 mols.). *p-n*-Propylbenzoic acid (m. p. 140—141°) was obtained in 1% yield. The *ketone*, which solidified when kept in the cold for some time, was obtained in 30% yield. It crystallised from methyl alcohol in white crystals, m. p. 69° (Found : C, 85·4; H, 8·1. $C_{19}H_{22}O$ requires C, 85·7; H, 8·2%), the *oxime* crystallised from light petroleum in white silky needles, m. p. 93° (Found : N, 4·99. $C_{19}H_{23}ON$ requires N, 4·98%), the *semicarbazone* crystallised from dilute alcohol in white needles, m. p. 122—123° (Found : C, 74·7; H, 7·8; N, 13·0. $C_{20}H_{25}ON_3$ requires C, 74·3; H, 7·7; N, 13·0%), and the p-*nitrophenylhydrazone* crystallised from alcohol in orange-yellow crystals, m. p. 126° (Found : C, 74·5; H, 6·6; N, 10·3. $C_{25}H_{27}O_2N_3$ requires C, 74·8; H, 6·7; N, 10·5%).

pp′-*Di*-n-*butylbenzophenone*. This was obtained from *n*-butylbenzene (27 g., 2 mol.), oxalyl chloride (12·5 g., 1 mol.), aluminium chloride (33·5 g., 2·5 mols.), and carbon disulphide (30 c.c.), in 40% yield, as a yellowish oil, b. p. 258—262°/26 mm. No acid could be isolated. The *oxime* crystallised from light petroleum in white crystals, m. p. 70—71° (Found : C, 81·1; H, 8·7. $C_{21}H_{27}ON$ requires C, 81·5; H, 8·7%), and the p-*nitrophenylhydrazone* crystallised from alcohol in orange-yellow crystals, m. p. 138° (Found : C, 75·2; H, 7·3; N, 9·4. $C_{27}H_{31}O_2N_3$ requires C, 75·5; H, 7·2; N, 9·7%).

n-*Alkylbenzoic acids*. Some of these acids have been prepared by oxidation of the corresponding

p-*n*-alkylphenyl methyl ketone with sodium hypobromite solution (Zaki and Fahim, *J.*, 1942, 307). They have also been obtained, in satisfactory yields, by a modification of the method described above for the preparation of the dialkylbenzophenones: a solution of the *n*-alkylbenzene (1 mol.) and oxalyl chloride (1 mol.) in carbon disulphide (4 mols.) was gradually treated with aluminium chloride (1 mol.) at room temperature, with stirring. The product was left overnight, carbon disulphide was removed, and the residue was decomposed with ice-cold water. The mass was collected and digested with hot N/2-sodium hydroxide for ½ hour. Any undissolved oil was extracted with ether and the acid precipitated on acidification.

p-*Ethylbenzoyl chloride*. This was obtained, by heating *p*-ethylbenzoic acid (9 g.) and thionyl chloride (13 g.) under reflux for 3½ hours, as a colourless fuming liquid, b. p. 235—236°. 1-p-*Ethylbenz*-2-p-*nitrophenylhydrazide* was obtained by heating under reflux for a short time an ethereal solution of equimolecular amounts of *p*-nitrophenylhydrazine and *p*-ethylbenzoyl chloride, filtering the solution from an insoluble product, and removing the solvent. The hydrazide crystallised from benzene–light petroleum in yellowish tiny needles, m. p. 220—221° (Found: C, 63·5; H, 5·3; N, 14·6. $C_{15}H_{15}O_3N_3$ requires C, 63·2; H, 5·3; N, 14·7%).

p-n-*Propylbenzoyl chloride*. Propylbenzoyl chloride, obtained by heating under reflux *n*-propylbenzoic acid (8 g.) and thionyl chloride (10 g.) for 4½ hours, was a yellowish fuming liquid, b. p. 135—136°/20 mm. The amide crystallised from benzene–light petroleum in white silky needles, m. p. 152° (Willard and Maresh, *J. Amer. Chem. Soc.*, 1940, **62**, 1253, give m. p. 128·4°) (Found: C, 73·8; H, 7·9; N, 8·4. Calc. for $C_{10}H_{13}ON$: C, 73·6; H, 7·9; N, 8·5%). N-*Methyl*-p-n-*propylbenzamide* was obtained by shaking together the cooled acid chloride and aqueous methylamine, and crystallised from benzene–light petroleum in white feathery-like crystals, m. p. 100—101° (Found: C, 74·5; H, 8·4; N, 8·2. $C_{11}H_{15}ON$ requires C, 74·5; H, 8·5; N, 7·9%). 1-p-n-*Propylbenz*-2-p-*nitrophenylhydrazide* crystallised from acetone–light petroleum in whitish crystals, m. p. 201° (Found: C, 64·4; H, 5·6; N, 14·3. $C_{16}H_{17}O_3N_3$ requires C, 64·2; H, 5·7; N, 14·0%).

p-n-*Butylbenzoyl chloride*. This was prepared by heating under reflux *n*-butylbenzoic acid (7·5 g.) and thionyl chloride (9 g.) for 4½ hours, and formed a yellowish liquid, b. p. 155—156°/26 mm. The amide crystallised from alcohol in white crystals, m. p. 136° (Willard and Maresh, *loc. cit.*, give m. p. 121·5°) (Found: C, 74·3; H, 8·2; N, 7·8. Calc. for $C_{11}H_{15}ON$: C, 74·5; H, 8·4; N, 7·9%). N-*Methyl*-p-n-*butylbenzamide* crystallised from benzene–light petroleum in white crystals, m. p. 70—71° (Found: C, 75·3; H, 9·0; N, 7·2. $C_{12}H_{17}ON$ requires C, 75·4; H, 8·9; N, 7·3%).—FOUAD I UNIVERSITY, FACULTY OF SCIENCE, ABBASSIA, CAIRO, EGYPT. [*Received, May 11th*, 1948.]

The Bromination of Dimethoxystilbenes. By FELIX BERGMANN.

IN our recent paper on this subject (*J.*, 1947, 1450) we stated that "in all known cases the speed of addition of bromine to the central double bond of a stilbene is greater than that of nuclear substitution". Prof. H. Erdtman calls our attention to the fact observed by him (*Ber.*, 1941, **74**, 50) that pinosylvine dimethyl ether (3 : 5-dimethoxystilbene) is dibrominated in the ring before saturation of the double bond. It is of great interest that introduction of a second methoxyl group into the anisole ring increases the rate of nuclear substitution over that of addition to the olefinic double bond. We regret having overlooked Erdtman's observation, the original publication of which was not available to us.—DEPARTMENT OF PHARMACOLOGY, THE HEBREW UNIVERSITY, JERUSALEM, ISRAEL. [*Received, May 6th*, 1948.]

The Occurrence and Significance of the Pentose Sugars in Nature, and their Relationship to the Hexoses.

THE HUGO MÜLLER LECTURE, DELIVERED BEFORE THE CHEMICAL SOCIETY ON MARCH 4TH, 1948.

By E. L. HIRST, M.A., D.Sc., F.R.S.

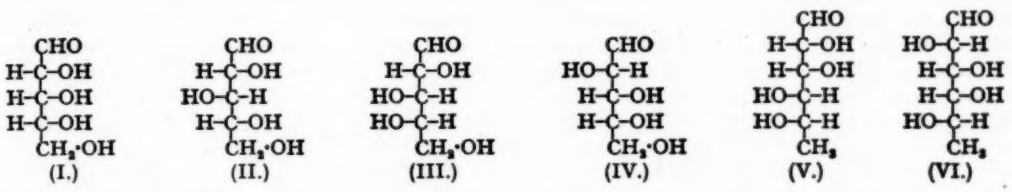
MODERN organic chemistry impinges in so many ways on botanical sciences that any chemist who is honoured by an invitation to deliver the Hugo Müller Lecture must be aware of many fields of investigation, each of which could serve as a subject for review fully compatible with the conditions attached to the lectureship. Even when the scope of inquiry is limited to the chemistry of the carbohydrates there still remains a wide range of problems which involve, at one and the same time, fundamental problems in both botany and chemistry. There are, for example, the many aspects of the problem of photosynthesis, and the multifarious questions relating to the structure and transformation products of the starches. These subjects, however, have been authoritatively reviewed within the past year or two, and it seemed opportune to use the present occasion for the discussion of certain problems connected with the pentose group of sugars. These questions, although clearly of great and increasing importance to both chemists and biologists, have not as yet passed beyond the initial stages of investigation, and, in consequence, it will be necessary to lay stress more on the nature of the problems which confront us than on clear cut solutions and generalisations.

The group of substances which are to be the main subject of discussion includes the four pentoses—xylose, lyxose, ribose, and arabinose—together with two methylpentoses, rhamnose and fucose. Considerable historical interest is attached to this group in view of the essential part its members played in the early development of carbohydrate chemistry when they were used in the elucidation of the stereochemistry of the hexoses. But at that time the main interest was centred on the hexoses themselves in view of the obvious importance of the many well-known natural products based on glucose, galactose, mannose, and fructose, and, in consequence, the pentoses were regarded as little more than chemical curiosities, despite the established occurrence of arabinose and xylose in certain plant materials. Later, when special attention was paid to the nature of the ring systems present in sugars, the problems presented by the pentoses were found to be somewhat simpler in character than those encountered in the hexose series, and it will be recalled that the occurrence of the pyranose ring in a stable carbohydrate derivative was, in fact, first demonstrated for the normal form of β-methylxyloside.[1]

In recent years, however, the widespread occurrence of the pentose sugars in Nature, and their importance in metabolism, have become increasingly manifest, and greater interest is now being taken in the study of these substances in their own right and not merely as aids or adjuncts to the chemistry of the hexoses. They occur, for example, as essential components of some members of the B group of vitamins and in certain of the co-enzymes present in systems responsible for oxidation and reduction. D-Ribose and its 2-deoxy-derivative are the carbohydrate components of the nucleic acids, the study of which is being so vigorously pursued today on account of their intimate connection with the chemistry of living processes. Pentose residues are encountered also in an astonishing variety of complex polysaccharides which act as food reserve materials in plant seeds. They are found in the cell walls of plants, and one of them plays a mysterious part in the chemical changes which result in lignification. It has been observed also that the new membrane formed in the course of cell division shows initially reactions which are characteristic of pectic materials, and the results of recent investigations suggest that pectic materials usually, and perhaps invariably, contain pentose constituents. It may well be therefore that pentose sugars play an essential part in this phase of cell division. As another example of their versatility it may be recalled that certain polysaccharides which contain pentose sugar residues in their molecular structure may function as water retaining materials of use to the germinating seed. In view of this wide range of uses and properties the biochemical importance of this group is unquestionable, and it appears appropriate to review briefly the ways in which the pentoses occur in Nature and to indicate such generalisations as have become apparent concerning their structure and their biochemical relationships.

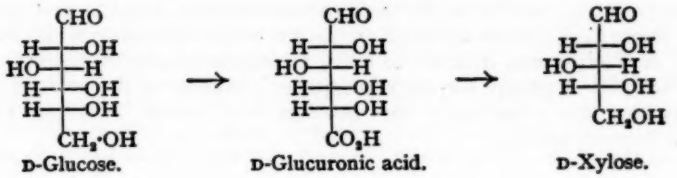
There are four possible aldopentoses and all of them are known; namely, arabinose, ribose,

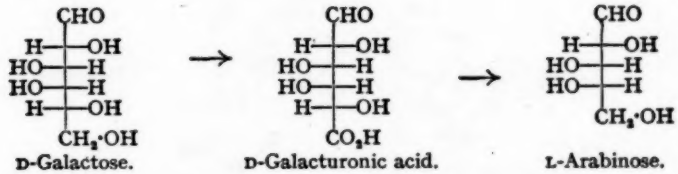
xylose, and lyxose. Each of them can exist in enantiomorphic D- and L-forms, but of these eight sugars we shall be concerned mainly with D-ribose (I), D-xylose (II), L-arabinose (III),



and D-arabinose (IV), together with the two methylpentoses L-rhamnose (V) and L-fucose (VI), the other modifications being rarely, if ever, encountered amongst natural products. A detailed study of the chemistry of these sugars has shown that they give rise to derivatives of the aldehyde form, and of both the pyranose and the furanose ring form. In general their chemical properties are very similar to those of the corresponding hexoses, but they appear on the whole to be somewhat more reactive. So far as our present knowledge extends, each of these sugars tends to occur in natural products in one preferred ring form. For example, ribose and arabinose are encountered in the furanose ring form, whilst xylose and rhamnose invariably occur as pyranose sugars.

Inspection of these formulæ reveals some interesting stereochemical relationships. D-Xylose is stereochemically very similar to D-glucose, and so is L-arabinose to D-galactose. In both pairs the hexose sugar could be transformed into the corresponding pentose by oxidation at C_6 to the uronic acid, followed by decarboxylation. Now it is significant that in the group of plant gums and mucilages one very frequently finds D-galacturonic acid associated with D-galactose and L-arabinose, and D-glucuronic acid with D-xylose and D-glucose. It must, therefore, be regarded as probable that these pentoses arise in Nature by a mechanism of this type. Nevertheless a detailed examination of the structures into which the various residues are incorporated shows that the transformations cannot take place at the polysaccharide level, but must involve preliminary degradation to monosaccharides after which new structures are built up. Much of the experimental work about to be mentioned had its origin in attempts to find an answer to this question of the origin of the pentoses.

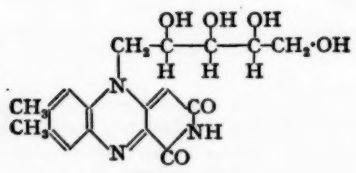




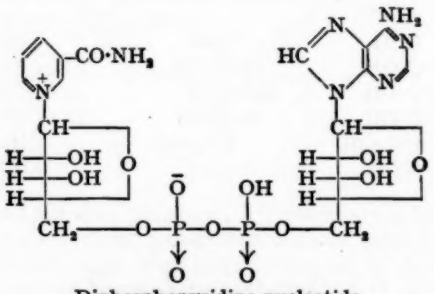
Among the pentose sugars, D-ribose occupies a special position in that it is the sugar present in nucleic acids, in certain co-enzymes and vitamins. For example it is found in a very unusual form, namely as the reduced ribityl residue, in riboflavin (6 : 7-dimethyl-9-D-ribityl*iso*alloxazine). Here we are concerned only with the chemistry of the sugar portion of the molecule, and it is significant that despite the absence of ring structure in the sugar the stereochemistry of the sugar residue is of great biological importance. Synthesis of analogous flavins containing other sugar residues gives rise to substances of quite different biological activity.

D-Ribofuranose residues are encountered in the diphosphopyridine nucleotide (co-enzyme I) [1] and in the nucleic acid group. The structures assigned have been arrived at on evidence based on degradations and methylation results. In some substances the nature of the ring system has been definitely ascertained, but it is clear that the chemistry of the nucleotides and nucleic acids requires much further exploration. Rapid advances are now being made as the result of

the synthetic work of Professor A. R. Todd and his colleagues at Cambridge, and recently these workers have succeeded in carrying through for the first time a synthesis of a naturally occurring

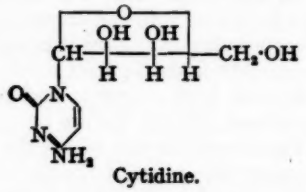


Riboflavin.



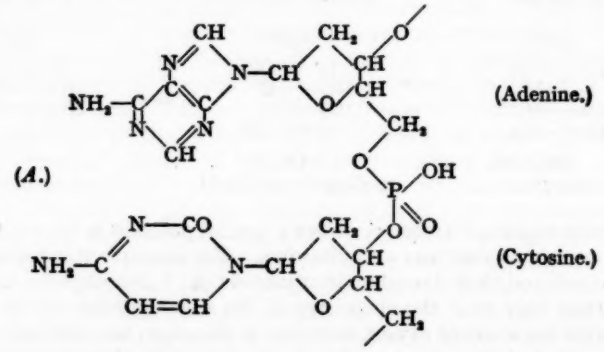
Diphosphopyridine nucleotide.

pyrimidine nucleoside (cytidine).[3] This involved the difficult feat of introducing the D-ribose residue in its furanose form, and now that this has been accomplished the way is open for further syntheses of nucleosides. Work in this field, it should be noted, involves all the difficulties inherent in the chemistry of those very labile substances, D-ribose and 2-deoxy-D-ribose, as well as those encountered in handling nitrogen glycosides.



Cytidine.

Some idea of the general nature of the polymeric nucleic acids has been gained by a combination of chemical and *X*-ray data (Astbury).[4] The diagram (*A*) indicates Astbury's views on the structure of nucleic acids based on deoxyribose. Here the mode of linkage of successive units is necessarily at C_5 and C_3 of the deoxyribose residues, but the problem is much more difficult for the ribose nucleic acids in which each sugar residue possesses an additional OH group. The evidence is conflicting and difficult to interpret owing largely to uncertainties concerning the rates of hydrolysis of phosphate ester groupings attached to the various OH groups, but according to Astbury the observed *X*-ray spacings tend rather to favour linkages through C_5 and C_3 (or perhaps C_5 and C_2).



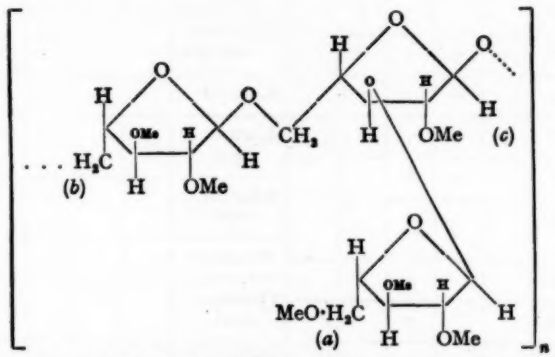
(Adenine.)

(Cytosine.)

(*A*.)

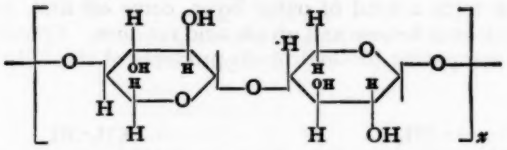
In the nucleic acids and nucleotides, ribose is not accompanied by other pentose sugars; these, however, occur very widely in plant products, notably in gums, mucilages, and pectic materials. The pentose sugars here involved are L-arabinose and D-xylose, and ribose is absent. Associated with the pentoses one frequently finds uronic acids (D-glucuronic, D-galacturonic) and hexose sugars, especially D-galactose, D-mannose, together with the methylpentoses L-rhamnose and L-fucose. The polysaccharide, araban,[5] which is found as a component of the pectic

material of many plants (for example ground nuts, sugar beet) may be taken as a simple example. It can be extracted from finely powdered ground nut,[6] after removal of the oil (by alcohol) and protein (by 10% aqueous sodium chloride), by treatment with dilute sodium hydroxide. This gives a mixture of pectic acid and araban which is extracted with alcohol, giving a crude araban still severely contaminated with pectic acid The pure araban is obtainable by regeneration of the free polysaccharide from its acetate. These operations are mentioned in order to illustrate one of the main difficulties encountered in this field of study, namely the isolation of pure homogeneous material suitable for structural investigations. The araban gives on methylation the dimethyl derivative, which in turn undergoes hydrolysis to 2 : 3 : 5-trimethyl, 2 : 3-dimethyl, and 2-methyl L-arabinose in equimolecular proportions. The ease of hydrolysis indicates that all the residues are furanose. These observations enable us to gain considerable insight into the general type of structure present in the araban, although they are insufficient to establish a single unique formula. The number of end groups (1 in 3) shows that a highly branched structure is present, and one of the very few structural formulæ which will fit the observations is shown below.[6]



(*a*) Gives 2 : 3 : 5-trimethyl, (*b*) gives 2 : 3-dimethyl, (*c*) gives 2-methyl L-arabinose.

At this stage one of the most important polysaccharides containing xylose may be briefly considered. This is the xylan or wood gum intimately associated with cellulose in woody tissues and found abundantly in wood, straw, esparto grass, oat-hulls, etc. It is extracted by alkali, but as normally isolated it contains residues of L-arabinose (3—8%) as well as of D-xylose. The main features of its structure are clear, since on methylation and hydrolysis it yields 2 : 3-dimethyl D-xylose, revealing thereby that it contains chains of 1 : 4-linked xylopyranose residues which are structurally analogous with the glucose chains in cellulose.[7] The molecular weight is fairly high, probably not less than 20,000. Much has still to be learned concerning the



fine structure. At one time the evidence seemed to indicate that L-arabofuranose residues terminated the chains of D-xylose units in xylan,[8] but it has recently been observed that the proportion of arabinose is variable, depending on the mode of extraction, and it has been found possible, by using only very gentle methods of purification, to obtain an undegraded xylan which contains no arabinose residues.[9] It seems likely, therefore, that xylan is composed solely of xylose units and that the arabinose normally associated with it occurs as an araban polysaccharide of the type we have just considered. Further evidence in favour of this view is the observation that, besides arabinose, the crude xylan contains D-galactose and D-galacturonic acid, typical of pectic materials.

It is only rarely, however, that plant polysaccharides are found containing one sugar residue only. In general, the structures display considerably greater complexity as will be apparent from Table I which indicates the sugar and uronic acid residues present in some typical gums and mucilages. When so many sugars are involved it becomes all the more difficult to be certain that

the material selected for examination is a single homogeneous substance. Fortunately, however, some of the gums (for example, that exuded by the damson tree) appear to possess an astonishingly invariable composition which facilitates examination. On the other hand there appear to be several types of gum arabic, differing in their arabinose content and possibly in other respects also.

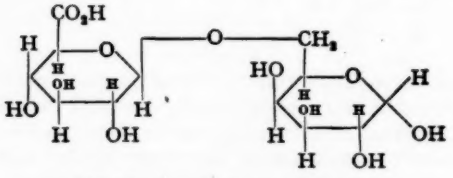
TABLE I.

Gum.	D-Glucuronic acid.	D-Galacturonic acid.	D-Galactose.	D-Mannose.	D-Xylose.	L-Arabinose.	L-Rhamnose.	L-Fucose.
Almond	+		+		+	+		
Arabic	+		+			+	+	
Cherry	+		+	+	+	+		
Cholla		+	+		+	+	+ ?	
Damson	+		+	+	+	+		
Egg plum	+		+		+	+		
Grape-fruit	+		+			+		
Lemon	+		+			+		
Mesquite	+*		+			+		
Orange	+		+			+		
Purple plum	+		+		+	+		

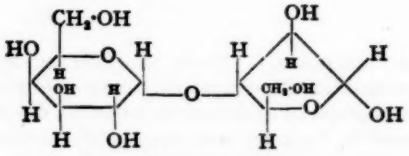
Mucilage.	D-Glucuronic acid.	D-Galacturonic acid.	D-Galactose.	D-Mannose.	D-Xylose.	L-Arabinose.	L-Rhamnose.	L-Fucose.
Brassica alba		+	+		+	+	+	
Lepidium sativum		+	+		+	+	+	
Linseed		+	+		+	+	+	
Locust bean			+	+				
Lucerne seed			+	+				
Plantago		+	+		+	+	+	
Quince seed		+			+	+		
Traga-canth		+	+		+	+		+
Ulmus fulva		+	+				+	

* Methoxy-derivative.

The presence of several different residues introduces additional complications into structural determinations, since questions concerning the order of arrangement of residues arise as with proteins. Progress has been made, however, by taking advantage of the fact that the different portions of the gum molecule are removed by hydrolysis at different rates. Usually the arabofuranose residues, which form a kind of outer layer, come off first, leaving a degraded gum containing the stable nucleus of hexose and uronic acid residues. Considerable information can, therefore, be gained by comparing the hydrolysis products of the fully methylated derivatives



Aldobionic acid from gum arabic.
(6-β-D-Glucuronosido-D-galactose.)
(VII.)



3-D-Galactosido-L-arabofuranose.
(VIII.)

of the original and the degraded gum, points of junction frequently becoming apparent in this way. These results give also the nature of the linkages whereby the various residues are bound in the polysaccharide. Sometimes it is possible to go further than this if conditions can be found for hydrolysis of the gum (or its methylated derivative) to oligosaccharides, for example aldobionic acids or disaccharides, the structures of which reveal at once how two of the residues are mutually

linked. Often, too, further information can be gained by a study of the oxidation of the gum by periodic acid and the identification of residues not attacked by the reagent.

In Table II some results are given for the hydrolysis of methylated derivatives of original and degraded gums. In the case of gum arabic it will be noted that an aldobionic acid (VII)

TABLE II.

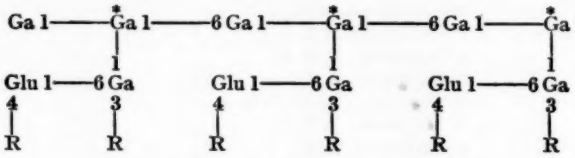
Hydrolysis Products from Methylated Gums.

Gum.	Methylated sugars.	Mode of attachment of residues in gum molecule.
Gum arabic [10]	L-Arabinose, 2, 3, 5	Al
	L-Arabinose, 2, 5	A^1_5
	D-Galactose, 2, 3, 4, 6	G_1
	D-Galactose, 2, 4	$6G^1_3$
	L-Rhamnose, 2, 3, 4	Rhl
	D-Glucuronic acid, 2, 3	Gl^1_4
Degraded gum arabic [11]	D-Galactose, 2, 3, 4, 6	Gl
	D-Galactose, 2, 3, 4	G^1_6
	D-Galactose, 2, 4	$6G^1_3$
	D-Glucuronic acid, 2, 3, 4	Gll
Damson gum [12]	L-Arabinose, 2, 3, 5	Al
	L-Arabinose, 2, 3	A^1_5
	D-Xylose, 2, 3, 4	Xl
	D-Galactose, 2, 4, 6	G^1_3
	D-Galactose, 2, 4	$6G^1_3$
	D-Galactose, 2	$^4G^1_3$
	D-Galactose, 4	$^3G^1_3$
	D-Mannose (dimethyl)	M?
	D-Glucuronic acid, 2, 3, 4	Gll
	D-Glucuronic acid, 2, 3	Gl^1_4
Degraded damson gum [13]	D-Galactose, 2, 3, 4, 6	Gl
	D-Galactose, 2, 3, 4	G^1_6
	D-Galactose, 2, 4, 6	G^1_3
	D-Galactose, 2, 4	$6G^1_3$
	D-Xylose, 2, 3, 4	X1
	D-Mannose (dimethyl)	M?
	D-Glucuronic acid, 2, 3, 4	Gll
	D-Glucuronic acid, 2, 3	Gl^1_4
Cherry gum [14]	L-Arabinose, 2, 3, 5	Al
	L-Arabinose, 2, 5	A^1_5
	D-Mannose (positions ?)	M?
	D-Galactose, 2, 4, 6	G^1_3
	D-Galactose, 2, 4	$6G^1_3$
	D-Glucuronic acid, 2, 3, 4	Gll
	D-Glucuronic acid, 2, 3	Gl^1_4
	(Methylated D-xylose)	X?
Egg plum (degraded) [15]	D-Galactose, 2, 3, 4, 6	Gl
	D-Galactose, 2, 3, 4	G^1_6
	D-Galactose, 2, 4, 6	G^1_3
	D-Galactose, 2, 4	$6G^1_3$
	D-Glucuronic acid (?)	Gl?
	(Aldobionic acid is 6-glucuronsidogalactose)	
Mesquite [16]	L-Arabinose, 2, 3, 5	Al
	L-Arabinose, 3, 5	A^1_5
	D-Galactose, 2, 4	$6G^1_3$
	D-Glucuronic acid, 2, 3, 4	Gll
	(Also a dimethyl methylhexoside)	
Tragacanthic acid [17]	D-Xylose, 2, 3, 4	X1
	D-Xylose, 3, 4	X^1_3
	L-Fucose, 2, 3, 4	Fl
	D-Galacturonic acid, 2, 3	Gal^1_4
	D-Galacturonic acid (monomethyl)	Gal?

(Gum tragacanth contains also a neutral araban.)

[A = L-Arabofuranose, G = D-Galactopyranose, M = D-Mannopyranose, X = D-Xylopyranose, Rh = L-Rhamnopyranose, F = L-Fucopyranose, Gl = D-Glucuronic acid (pyranose), Gal = D-Galacturonic acid (pyranose)].

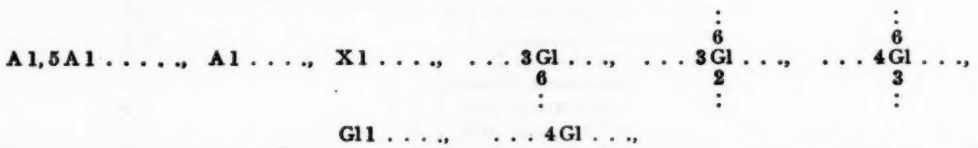
having the structure of 6-glucuronosidogalactose [18] reveals part of the gum's molecular architecture. The arabinose residues are present either as end groups united only by their reducing groups to the rest of the gum (A1 . . .) or doubly involved by links at C_1 and C_3 (. . . 3A1 . . .). Strangely enough, damson gum has an entirely different aldobionic acid residue (2-glucuronosidomannose), and its non-terminal arabofuranose residues are of the type . . . 5A1 . . . Returning for a moment to gum arabic and continuing the account of F. Smith's work on this polysaccharide, one may note that further insight into its structure was gained by the discovery of a disaccharide (3-galactosidoarabinose) [19] (VIII) as a product of partial hydrolysis. Armed with these various items of information Smith has been able to give the general outline of the structure and to eliminate all but a few closely similar alternative formulations.[20] The structure suggested is shown in (IX) where the backbone or main chain of galactose residues with 1:3 and 1:6 linkages—a common feature in plant gum structures—is apparent together with the various groupings attached as side chains.



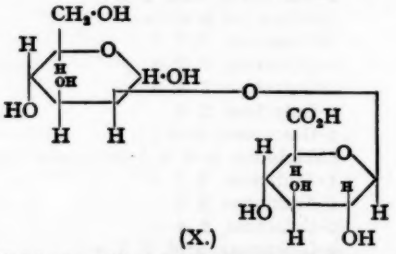
(IX.) Smith's formula for gum arabic.

Ga = D-Galactopyranose, Glu = D-glucuronic acid. The unspecified linkages at Ga* are either 3 and 6, or 6 and 3 respectively, but precise assignment is not yet possible. The R groups are (1) A1, where A is L-arabofuranose, (2) Rh1, where Rh is L-rhamnopyranose, and (3) Ga 1—3A1. The individual points of attachment of the various R groups are at present uncertain.

Damson gum is decidedly more complicated, as will be seen from Table II, both with respect to the degraded and to the undegraded gum, and methylation studies have revealed that the following residues are incorporated in the molecular structure :



together with mannose residues of as yet unknown linkage (where A = L-arabofuranose, X = D-xylopyranose, G = D-galactose, and Gl = D-glucuronic acid, linked as shown). Here again the pentose residues are present in the outer structure of the branched molecule and are readily removed. It is probable also that the main backbone of the molecule is a chain of D-galactose residues with 1 : 3- and 1 : 6-linkages. The aldobionic acid (X), which comprises



(X.)

Aldobionic acid from damson gum/cherry gum.

one of the most stable structural elements is 2-glucuronosidomannose, which is present also in cherry gum. No detailed formula for these gums can, however, be advanced at present, and it is clear that new methods of attack will be required before the problem can be fully solved.

Information is gradually being accumulated concerning other gums, and although it is clear that they vary considerably in structure, the possession of easily removable pentose residues is a general feature. Some of the observations are summarised in Table II which gives the hydrolysis products isolated from some methylated gums and the points of attachment of the corresponding sugar residues in the gum.

Mesquite gum [16] is a particularly interesting case. This contains arabinose, galactose, and a uronic acid containing a methoxyl residue. On gentle hydrolysis only the labile arabofuranose residues are eliminated. Two aldobionic acids, both of them methylated, have been isolated (6-glucuronosidogalactose and 4-glucuronosidogalactose). The main structure to which the pentose residues are attached is a branched chain of galactose and methylated glucuronic acid residues, with the latter linked to C_3 and C_6 of galactose residues.

Gum tragacanth,[17] the exudate of *Astragalus* species (leguminosæ), is a complex mixture, comprising an araban and an acidic polysaccharide tragacanthic acid. The latter contains residues of the pentose, D-xylose (some attached as end groups), and the methylpentose, L-fucose, which is more commonly found in seaweeds. This again occurs, partly at least, as an

TABLE III.

Hydrolysis Products from Methylated Mucilages

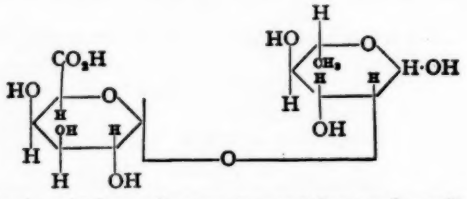
Mucilage.	Methylated sugars.	Mode of attachment of residues in mucilage molecule.
Salep mannan [21]	D-Mannose, 2, 3, 6	M^1_4
	D-Mannose, 2, 3, 4, 6	M1
Gum gatto [22] (locust bean) ...	D-Galactose, 2, 3, 4, 6	G1
	D-Mannose, 2, 3, 6	M^1_4
	D-Mannose, 2, 3	$6M^1_4$
Lucerne seed [23]	D-Galactose, 2, 3, 4, 6	G1
	D-Galactose, 2, 4, 6	G^1_3
	D-Mannose, 3, 4	$6M^1_3$
Plantago lanceolata [24] (seed)	D-Galactose, 2, 3, 4, 6	G1
	D-Galactose, 2, 4, 6	G^1_3
	D-Xylose, 2, 3, 4	X1
	D-Xylose, 2, 4	X^1_3
	D-Xylose, 2, 3	X^1_4
	D-Xylose, 2	$4X^1_2$
	D-Xylose, 3	$4X^1_3$
	D-Xylose unmethylated	$^3_4X^1_2$
* (Also methylated derivatives of L-arabinose, L-rhamnose, and D-galacturonic acid.)		
Plantago ovata [25] (seed)	L-Arabinose, 2, 3, 5	A1
	D-Xylose, 2, 3, 4	X1
	D-Xylose, 2, 4	X^1_3
	D-Xylose, 2	$4X^1_2$
	D-Xylose, 3	$4X^1_3$
	D-Xylose, unmethylated	$^3_4X^1_2$
(Methylated D-galacturonic acid and methylated L-rhamnose, combined as galacturonosido-2-rhamnose.)		
Ulmus fulva [26] (bark)	D-Galactose, 2, 3, 4, 6	G1
	D-Galactose, 2, 4, 6	G^1_3
	D-Galactose, 2, 3, 6	G^1_4
	L-Rhamnose, 3, 4	Rh^1_2
	L-Rhamnose, 4	$3Rh^1_2$
	L-Rhamnose, unmethylated	$^3_4Rh^1_2$
	D-Galacturonic acid, 2, 3, 4	Gal 1
	D-Galacturonic acid, 2, 3	Gal $^1_4$

end group. The uronic acid is D-galacturonic, and the occurrence of this in place of D-glucuronic acid stresses the peculiarity of this gum and aligns it rather with the plant mucilages.

No doubt many such intermediate substances will be encountered, but on the whole it will be seen from Tables I and III that D-galacturonic acid tends to be characteristic of the plant mucilages. Some of these, for example salep mannan [21] (which in structure recalls ivory-nut mannan,[27] having chains of 1 : 4-linked β-D-mannose residues), the mannogalactan gum gatto (locust-bean mucilage),[22] and the mannogalactan of lucerne seed,[23] contain no pentose residues. It is clear, therefore, that the mucilaginous properties of these substances are not necessarily bound up with their pentose components. Mannogalactans are indeed of common occurrence (guar, Kentucky coffee bean, honey locust, foenugreek, gum tragon, to name only a few), but, nevertheless, mucilages in general are much more complex, and there is a pronounced tendency for D-galactose, D-galacturonic acid, and L-arabinose residues to occur together. The simultaneous occurrence of D-xylose and D-galactose is less common, but is notable in the case

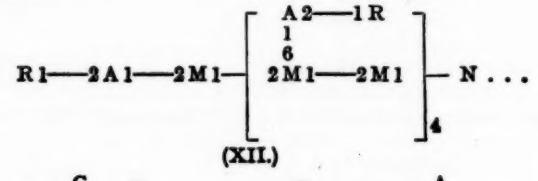
of the *Plantago* mucilages (Table III). These mucilages are remarkable for the complexity of their structure, containing galactose, galacturonic acid, xylose, and possibly both arabinose and methylpentose residues. The xylose residues are combined in the mucilage in the most diverse ways. Examination of the methylated mucilage from the seeds of *Plantago lanceolata* [24] has revealed that xylose residues are present linked through C_1 (end groups), through C_1 and C_3, through C_1 and C_4, through C_1, C_3, and C_4, through C_1, C_2, and C_4, and through C_1, C_2, C_3, and C_4. Somewhat similar results were obtained with *P. arenaria*,[25] the mucilage of which gives rise to an unusual aldobionic acid which is a D-galacturonosido-D-xylose, whilst *P. ovata* yields D-galacturonosido-2-L-rhamnose.[25]

Many more examples of mucilages could be given in which xylose, arabinose, galactose, and galacturonic acid residues occur together (*e.g.*, cress seed, white mustard seed), but it must

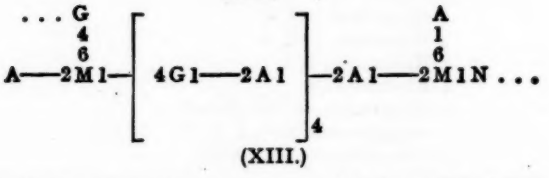


Aldobionic acid from slippery-elm and flax-seed mucilage.
(XI.)

suffice to remark upon a tendency for the pentose residues to be replaced wholly or in part by methyl pentose (L-rhamnose). This is seen in flax-seed mucilage [29] (residues, D-xylose, L-rhamnose, L-galactose, and D-galacturonic acid, with D-galacturonosido-2-L-rhamnose as the aldobionic acid), where the occurrence of L-galactose is noteworthy and is reminiscent of agar. L-Rhamnose is found also as a major constituent of the mucilage from the bark of *Ulmus fulva* [26] (slippery elm), where it occurs with D-galactose, D-xylose, and D-galacturonic acid. The aldobionic acid is D-galacturonosido-2-L-rhamnose (XI), and this mucilage is remarkable for containing residues of L-rhamnose in which every available hydroxyl group is involved in linkages with other residues. Very few examples of such complete substitution are known, but it occurs also in the *Plantago* mucilages (xylose) and in D-mannose residues present in the polysaccharide constituent of ovomucoid.



(XII.)



(XIII.)

We have already noticed an exception to the rule that one only of the enantiomorphs of each sugar is favoured in Nature in the occurrence of L-galactose in certain mucilages in place of the normal D-galactose. An even more remarkable case has recently come to light in Heidelberger's study of the polysaccharides associated with *Mycobacterium tuberculosis*.[30] From the somatic part of the bacterium a polysaccharide has been isolated which contains D-arabinose. It is found in this important biological polysaccharide together with L-rhamnopyranose, D-mannopyranose, and D-glucosamine (all normal stereochemically with the exception of the D-arabinose). An indication (XII) of the type of structural unit present has been given by Sir Norman Haworth and Professor Stacey.[31] D-Arabinose residues are found also in a polysaccharide which is associated with the waxes of *M. tuberculosis*, the accompanying residues in this case being D-galactopyranose, D-mannopyranose, and D-glucosamine (XIII).[32] Clearly this appearance of D-arabofuranose residues in so active a bacterium is highly significant, and the discovery may lead to important developments in our knowledge of metabolic processes.

These examples show how widely distributed in Nature the pentose sugars are and how important a part they play as component structural units of many complex polysaccharides. Their mode of occurrence reveals such a bewildering variety of links both with themselves and with other sugar residues that generalisations are almost impossible to discern at the present stage of investigation. Some regularities do nevertheless emerge. There are, for example, preferred types of ring structure assumed by the various pentoses in combining to give polysaccharides. For D-xylose this is the pyranose modification, and no evidence has yet been obtained of the occurrence of xylofuranose residues in hemicelluloses, gums, or mucilages. But these xylopyranose residues can take part in polysaccharide formation in an astonishing variety of ways, sometimes as end groups linked to other residues only through the reducing groups, sometimes doubly linked through C_2, C_3, or C_4 in addition to C_1 or trebly linked, involving a branched chain, through C_1, C_3, and C_4. Most frequently the residue to which the xylose is directly linked is another reducing sugar, usually xylose, glucose, or galactose, but sometimes xylose is found as one of the residues in an aldobionic acid, the other portion being glucuronic or galacturonic acid.

L-Arabinose is almost equally versatile in its modes of combination, but this sugar is normally encountered in the five-membered ring form, and in the polysaccharides in which it occurs it is present exclusively in the form of arabofuranose residues. This generalisation holds also for the D-variety of the sugar which is encountered in the furanose form as a constituent of the bacterial polysaccharides. It may be noted in passing that the occurrence of arabinose in both the D- and the L-modification is of special interest in view of the close stereochemical relationships between arabinose and galactose which is also found in Nature in both the D- and the L-form. On the other hand xylose and the correspondingly related hexose, glucose, display no such tendency to occur in more than one of the possible enantiomorphic forms, and this applies also to rhamnose and fucose. In the polysaccharides, residues of L-arabinose are linked sometimes exclusively to other arabinose residues as in the highly branched molecule of the polysaccharide araban, which possesses arabofuranose units linked through C_1 in three different ways, namely through C_1 (end group), through C_1 and C_5 (unbranched union), and through C_1, C_2, and C_5 (branched chain) respectively, but more frequently they are attached to other sugar residues, particularly galactose. In the plant gums there are arabinose residues present as end groups linked only through C_1, residues forming part of unbranched chains with links involving C_1 and C_5, and C_1 and C_3, and residues at which branching of the chain occurs with links involving three points of junction. The arabinose units are mostly, if not entirely, in the outer portions of the gum molecule, and we have at least a hint from the little that is so far known of the structural chemistry of the gums that many of these polysaccharides contain as backbone a chain of galactopyranose residues linked through their 1, 6, and 1 : 3 positions to which are attached uronic acid and pentose residues in the form of side chains.

Ribose and its 2-deoxy-derivative occupy a somewhat isolated position in our review. They occur in the D-forms, and so far as is known always in the furanose ring modification. They are the special sugars of the important group of nucleic acids, and seem to disdain admixture with their commoner relatives, with the result that little or nothing can be said regarding possible phytochemical inter-relationships with either the pentose or the hexose series of sugars. One faint hint may perhaps be found in the frequent occurrence of the 2-deoxy-form of ribose. The carbon atom involved here is the labile C_2 which can so readily undergo a Walden inversion and there may be, therefore, just a possibility that D-ribose is related *via* D-arabinose to L-galactose as its ultimate source.

The methyl pentoses, L-rhamnose and L-fucose, offer equally puzzling problems. Rhamnose occurs as the L-form, and so far as is known at present always as a pyranose residue. Its stereochemical pattern places it with L-mannose, but despite much speculation nothing is known with certainty regarding its biochemical relationship to other sugars. It is found in some polysaccharides united through its second carbon atom to the reducing group of galacturonic acid. It is curious, but whether significant or not cannot be estimated at present, that mannose which is closely related stereochemically to rhamnose is found in both cherry gum and damson gum united through its C_2 position to a uronic acid residue. L-Rhamnose also occurs doubly linked to other units through the C_1 and C_2 positions and trebly through C_1, C_2, and C_3, as for example in slippery-elm mucilage. Very little, however, is yet known of the range and variety of the linkages in which rhamnose can participate in plant mucilages, or of the mode of junction of fucose units in seaweed polysaccharides, and it is only too clear that much exploratory work remains to be done in these fields.

One general conclusion which can be drawn with reasonable certainty from the knowledge

gained concerning the molecular structures of the gums, pectins, and mucilages is that the transformation into pentosans of polysaccharides built up of hexose residues cannot take place in the plant at the polysaccharide level by way of oxidation at the C_6 position of the hexose residues with formation of uronic acid units, which on decarboxylation would yield pentose residues. The structures of the galactans, for example, differ so fundamentally from those of the gums and polyuronides based on D-galacturonic acid, and the latter are so far removed structurally from the arabans and from the L-arabinose residues present in the gums, that it is necessary to regard each polysaccharide as built up unit by unit by its own enzyme system. No such simple change, at the polysaccharide level, as galactan $\longrightarrow$ polyuronide $\longrightarrow$ araban is possible. The position rather seems to be analogous to that observed for starch in the course of the work of Hanes and Peat, where the transformation of amylose into amylopectin involves degradation followed by re-synthesis. It is certain, however, that for the gums and mucilages the changes necessary are much more drastic, involving the complete disintegration of one polysacharide, which may perhaps be starch, with transformation of hexoses, by way of the uronic acids, into pentoses, followed by re-synthesis. In view of the frequency with which D-galactose, D-galacturonic acid, and L-arabinose are encountered together in this group it is difficult to avoid the conclusion that L-arabinose does in fact stand in close phytochemical relationship to D-galacturonic acid and D-galactose (but we have to confess complete ignorance of the biochemical inter-relationships of D-glucose and D-galactose). Nothing is known, moreover, of the nature of the enzyme systems responsible for the synthesis of the gums and mucilages, but in view of the mass of evidence which has been accumulating in recent years concerning the importance and versatility of hexose-1 phosphates and phosphorylase enzyme systems in the synthesis of starch and glycogen (Cori, Hanes, Peat) and various disaccharides (Hassid), it would not be surprising to find similar mechanisms in operation here also.

If it is true that few generalisations can yet be made covering the occurrence and the mode of linkage of the various pentose sugars in natural products, still less is it possible to draw general conclusions concerning the functional significance of these substances in the economy of Nature. At first sight it might be thought that the bewildering variety of sugar residues and the complexity of their arrangement in the gums might denote a haphazard piecing together of unwanted molecular species, yet such evidence as is available has led my colleague Dr. J. K. N. Jones to the view that the composition of the individual gums is so specific and invariable that a knowledge of the sugars involved and of their quantitative relationships, such as may now be obtained rapidly by the use of the paper chromatogram, may suffice to identify the botanical species or even the variety of the plant which produced the gum.

Many of these gums are produced by the plant in response to a stimulus resulting from injury, and once formed they serve as a protective layer which seals off the living portion of the plant.[33] The movement of the gummy material can be traced, and its formation, in some cases at any rate, is said to coincide with cytoplasmic changes which involve the disappearance of starch granules. The quantity of gum is on occasions so great that it appears likely that the plant can mobilise the necessary carbohydrate materials at or near the point of injury. The inference is that the actual precursor of the gum may be glucose (or fructose), but no hint has yet been obtained of the mechanism of the changes which give rise to the arabinose, xylose, galactose, mannose, and uronic acid residues which are built up into the molecular structure of the gum. Furthermore, the particular functions served by the pentose residues remain quite obscure unless perhaps it is that their presence renders the protective mass less susceptible to the ordinary forms of attack by micro-organisms. There is, on the other hand, no convincing evidence that the plant gums themselves have their origin in the synthetic activities of micro-organisms which have invaded the plant tissues.

Little more is known concerning the part played in plant metabolism by the pentose residues present in the pectins and mucilages. Very often these materials appear to be part of the food reserve of the plant, but it is not clear what special function is to be attributed to the pentose constituents when these reserves are mobilised by an initial process of hydrolysis for use by the growing plant. One has to envisage indeed a wide variety of activities in which the pentose components appear to play an essential part. For example it is clear that very different metabolic roles are played by the pectic substances which occur in the middle lamella of flax fibres, by those present in the seed of the ground nut, and by the pentose residues in the mucilages which occur in the outer coat of quince or cress seeds and may be concerned in the maintenance of moist conditions round the seed by virtue of their power to absorb water. Very different again from any of these are the functions of the ribose or deoxyribose residues in the nucleic acids, and here the very special and highly specific occurrence of ribose as the carbohydrate of

this important group of substances presents one of the most baffling of problems, and one for which no solution can as yet be offered. The recent *X*-ray studies of Astbury and his colleagues on the structure of the macromolecules of the nucleic acids may perhaps give hints concerning the possible lines of inquiry here arising out of the conditions which have to be satisfied in the geometrical arrangement of the residues in the polynucleotides. It will be recalled that, in commenting on the relationship between the spacings in the proteins and those in the nucleic acids, Astbury referred to the flatness of the furanose ring of the ribose residue and its importance in the general building up of the long chains of nucleotides. But the chemist is unable to say why the dimensions of ribose residue or its configuration should be particularly favourable in this respect. Further investigations into the chemistry of ribose may give a clue, but for the present we must leave the problem there.

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OBITUARY NOTICES.

EINAR CHRISTIAN SAXTORPH BIILMANN.

1873—1946

EINAR CHRISTIAN SAXTORPH BIILMANN, whose death occurred on August 9th, 1946, was born in Frederiksberg, Copenhagen, on May 10th, 1873. He was the son of Sylvester Biilmann, a military veterinary surgeon, and his wife Atka Castberg. He matriculated in 1891 in classics, and in after life he maintained that it was an advantage for science students to have a classical education since a knowledge of Latin and Greek was useful to chemists and prevented them from having too narrow an outlook on life. He entered the University as a medical student, but in his first year his interest in the natural sciences was aroused, and in 1893 he passed the entrance examination to the Royal Polytechnical School. He did not, however, leave the University, and in 1897 he graduated with the degree of M.Sc. in chemistry.

Chemistry at this time in Denmark was dominated by two outstanding figures—Julius Thomsen, the thermo-chemist, and S. M. Jørgensen, the exponent of classical inorganic chemistry. Biilmann was much influenced by Jørgensen, and in 1898 he was appointed by him as an assistant in the Royal Polytechnical School. His first original work, obviously suggested by Jørgensen, described the preparation of sodium cobaltinitrite and its use as a reagent for potassium. His interest in organic chemistry was, however, aroused by the offer by the University of Copenhagen of a prize for a method for the preparation of acrylic acid from allyl alcohol. His thesis won for him a gold medal. He was encouraged to devote his attention to organic chemistry by Jørgensen, who pointed out to him that since the death of Zeise in 1847 no Dane had made any notable contribution to its advancement. Biilmann's next work was a continuation of Zeise's study of the thiols and xanthic acid, and in 1904 he obtained the degree of D.Phil. with a thesis entitled " Studier over organiske Svolvforbindelser."

After taking his doctor's degree Biilmann spent a year in Emil Fischer's laboratory in Berlin, but the conditions there were not congenial to him although this short stay undoubtedly influenced considerably his future career. He found little sympathy in the Berlin laboratory for the independent worker, the research worker being required to work under the close direction and supervision of Fischer's assistants. He felt also the lack of opportunity for discussion and exchange of ideas. Biilmann never worked in any of Fischer's fields of research, although later he criticised very severely his theory of the Walden inversion.

Shortly after his return to Copenhagen the chair of chemistry in the University became vacant by the death of Emil Petersen who had succeeded Julius Thomsen in 1901, and in 1907 Biilmann was appointed to the chair. His appointment led to a complete revolution in the teaching of organic chemistry in Denmark. Previously there had been no laboratory in the University for the teaching of organic chemistry, and after visits to England, Germany, and Switzerland he equipped a laboratory for this purpose. Biilmann was an inspiring lecturer, and his lectures were always well attended. He also took an active part in University administration, being elected in 1911 a member of the Consistory, and he continued to be a member until his retirement in 1943. During the years 1921—22 he was Rector Magnificus, and he filled this high office with great dignity. He took part in the organisation of international congresses, and he was one of the Danish representatives at the Rome meeting in 1920 when the International Union for Pure and Applied Chemistry was formed. His linguistic ability enabled him to take an active part in such international gatherings, and he was a Vice-President of the Union from 1922 to 1925 and President from 1928 to 1934. During his period of office the difficult question of the readmission of Germany and Austria fell to be decided, and there is no doubt that it was largely due to his tact that a satisfactory decision was reached.

In spite of heavy administrative duties Biilmann never lost his interest in research. To pure organic chemistry his main contribution was his work on the isomeric cinnamic and *allo*-cinnamic acids. By an ingenious series of experiments he was able to show that the three different *allo*cinnamic acids were not isomeric but polymorphic forms of *cis*-β-phenylacrylic acid. Many years later he returned to the subject of the spontaneous inoculation of molten substances with crystal nuclei as an experimental method for distinguishing between isomeric and polymorphic forms.

Although essentially an organic chemist, Biilmann recognised the valuable part which physical measurements could play in solving the problems of organic chemistry. During his study of the addition of mercury salts to unsaturated organic compounds he made use of

electrometric measurements in determining the complexity of the substances formed, a technique not previously applied in this field. He realised that the method might have a wide application and that it might be possible to elaborate a more convenient tool than the hydrogen electrode developed by S. P. L. Sørensen in 1908 in his classical work. In 1920 Biilmann suggested making use of the equilibrium system quinol $\rightleftharpoons$ benzoquinone + 2H—the quinhydrone electrode—and this was his most outstanding contribution to science. Biilmann's quinhydrone electrode was found to be extremely convenient in use, more especially by soil chemists, for the determination of hydrogen-ion concentration, and although it has now been largely replaced by the glass electrode this does not diminish the value of his contribution. Biilmann recognised the importance of the application of his method for the determination of the oxidation potential of many systems such as alloxan–dialuric acid and azo–hydrazo-compounds, and in a series of brilliant papers he described various methods for its determination. In 1928 he summarised his work in a paper read to the Faraday Society. He was a pioneer in the determination of redox-potential, now a familiar laboratory method.

Biilmann's services to science received wide recognition. He was a member of the Royal Danish Academy and of a number of foreign chemical societies.

In 1899 he married Valborg Gyring Nielsen, who, with a son and two daughters, survives him.

STIG VEIBEL.
J. L. SIMONSEN.

FRANCIS HENRY SWINDEN CURD.

1909—1948.

FRANCIS HENRY SWINDEN CURD was born at Loughton, Essex, on June 15th, 1909. His tragic death in hospital on December 2nd, 1948, from injuries sustained two days earlier in a railway collision at Stockport, Cheshire, cut short a career of splendid achievement and continuing promise.

Curd's earlier life was spent in Essex. He went to the Colchester Grammar School during 1917—18 and then to Bancroft's School, Woodford, in 1919, matriculating there in 1926 and passing to the Honours Chemistry School at Queen Mary (then East London) College. Curd took the final honours examination in June 1929, and then began research work at the College under Dr. Alexander Robertson, now Professor of Organic Chemistry at Liverpool University. When Robertson moved to the London School of Hygiene and Tropical Medicine in 1930, Curd went with him and continued his researches until late in 1933. The initial researches on ketones derived from phloroglucinol, although relatively unambitious, led to a clarification of anomalous results obtained by the cyclisation of aromatic *o*-hydroxy-ketones and also anomalies in the application of the von Pechmann and Simonis reactions to mono- and poly-hydric phenols. The later and more important researches were concerned primarily with the chemistry and structure of usnic acid and the lichen acids, and were published in a series of papers jointly with Robertson (1933, 1935, 1936, 1937). The work culminated in the development for usnic acid and its derivatives of entirely new structures which explained fully the reactions of the compounds, and which were later confirmed by Schopf. Professor Robertson speaks with the highest praise of Curd's careful and systematic experimental work throughout that period, and confesses that there have been many occasions since then " when in sticky researches I wished I could have had Curd's help as a collaborator ". The pertinacity in face of a troublesome research problem which Robertson's tribute implies was shown on many occasions during Curd's career in industry. He was elected a Fellow of the Chemical Society in 1929, and was granted his Ph.D. by London University in 1932.

At the end of 1933 Curd joined the staff of the Dyestuffs Division of Imperial Chemical Industries Limited, and began his industrial career in their research laboratories at Blackley, Manchester, where he worked until his death. His new colleagues were soon attracted by Curd's shy modesty and charm of manner, and from the outset all were greatly impressed by the neatness and precision of his laboratory technique. After observing Curd's response to the industrial research problems of his first few months a senior colleague recorded at the time : " his resourcefulness and ingenuity with these suggests that he will prove a fruitful research worker "—an assessment which was to be amply justified.

In the first few years of his industrial career Curd carried out researches on a variety of dyestuff problems, particularly in the azine series and on the chemistry of proflavine and acriflavine. He made inventive contributions during this period, but it was primarily a time of growth in technique and increasing grasp of the relationship between pure and applied

chemistry. When his Company decided in late 1937 to enter the field of chemotherapy by the hard way of pioneer research and invention, it is not surprising that Curd was chosen as a member of the initial team which was so carefully picked for this difficult task. He had already shown the appropriate temperament and skill in equally difficult but less fashionable fields of chemical research.

Curd set out with enthusiasm in early 1938 to survey and master the published literature on the chemotherapy of malaria and related aspects of tropical medicine as a preparation for original research work. The constitution of the relatively new German drugs atebrin (mepacrine) and plasmochin had not been clearly published at that time. During this phase of self-preparation Curd satisfied himself of the constitution of the German drugs by unequivocal synthesis and an exploration of various synthetic routes to these and related compounds. Thus it came about that as the war in the East developed and created the urgent need for synthetic antimalarials it was on the basis of Curd's experimental work that it became possible to begin the first British manufacture of mepacrine quickly and effectively in 1940. This necessary wartime deviation from the pioneer research work originally envisaged was only a temporary one, and at the earliest opportunity Curd and his colleague, F. L. Rose, returned to the search for antimalarial compounds having lower toxicity than mepacrine and having genuine prophylactic properties in addition to curative properties. By 1942 Curd and Rose had a considerable chemical team working with them, and the work progressed in close collaboration with their biologist colleague, D. Garnet Davey. The culmination of these efforts in the discovery of "Paludrine" has been fully recorded in the Warrington Yorke Memorial Volume of the Annals of Tropical Medicine, 1945. The contributions of these researches to the chemistry of pyrimidines, quinoxalines, and a variety of alkyldiguanides are considerable and have been published in more than thirty papers by Curd and Rose and their co-workers (1946—48). For his important rôle in these antimalarial researches Curd was awarded in 1947 the Gold Medal for Chemotherapy by the Worshipful Society of Apothecaries. His colleagues, Davey and Rose, received this considerable honour at the same time.

Following the discovery of "Paludrine", Curd led his chemical team in 1947 to a renewed and more intensive study of the chemotherapy of trypanosomiasis, again in collaboration with his biologist colleague Davey. This work led ultimately to an investigation of 4-amino-6-(2′-amino-6′-methylpyrimidyl-4′-amino)quinaldine 1 : 1-dimetho-salts, and culminated in the discovery of the new drug "Antrycide". It is hoped that the whole chemical background of this work will be published in due course. Meanwhile, the announcement by the Colonial Office in December 1948, following field trials in Africa, of the great promise of this new drug against trypanosomiasis in cattle is sufficient indication of the solid achievements of Curd's last researches.

It is some consolation to his colleagues that in the few weeks before his death Curd had the satisfaction of knowing from the field results coming in from Africa that success against trypanosomiasis was in sight. His tragic and early death is a severe personal blow to all those associated with him in industry, and he is mourned too in many academic laboratories where he was a frequent and welcome visitor. His charm, integrity, and ability were great, and his powers of leadership were progressively maturing. Indeed, Curd was in many ways an ideal industrial research man. Whilst he was a genuine scientist acceptable as such in any company concerned with pure science, he had a real understanding of applied chemistry and its objectives and of the manifold problems of technology associated with the development of a new discovery. That he would have continued to grow in stature and scope is not in doubt.

Curd leaves a wife and three young children to whom he was devoted. In private life he was a man of quiet but discriminating tastes, a keen gardener, and a lover of cricket. During a staff cricket match in his earlier years many of us were delighted to observe that his batsmanship had the same neat elegance as his laboratory technique. Both were indeed a characteristic expression of the man himself.

Curd was a devout Churchman and had been an active worker in the Church of England since his earliest Essex days. The Rev. Dr. Wilfred Garlick who had known him well as a churchman for many years writes: "I don't think Curd has ever been one of those who felt that the gap between religion and science was insurmountable. And he did not resolve the dilemma by a dichotomy which placed the two in separate compartments. He felt most keenly that the greater was man's knowledge, the greater was his need for a philosophy of a good life, and *that* he felt was provided absolutely by Christianity. He was a man of vision and integrity of life and purpose". Those of us who knew him best in the industrial sphere would not quarrel with that judgment.

C. PAINE.

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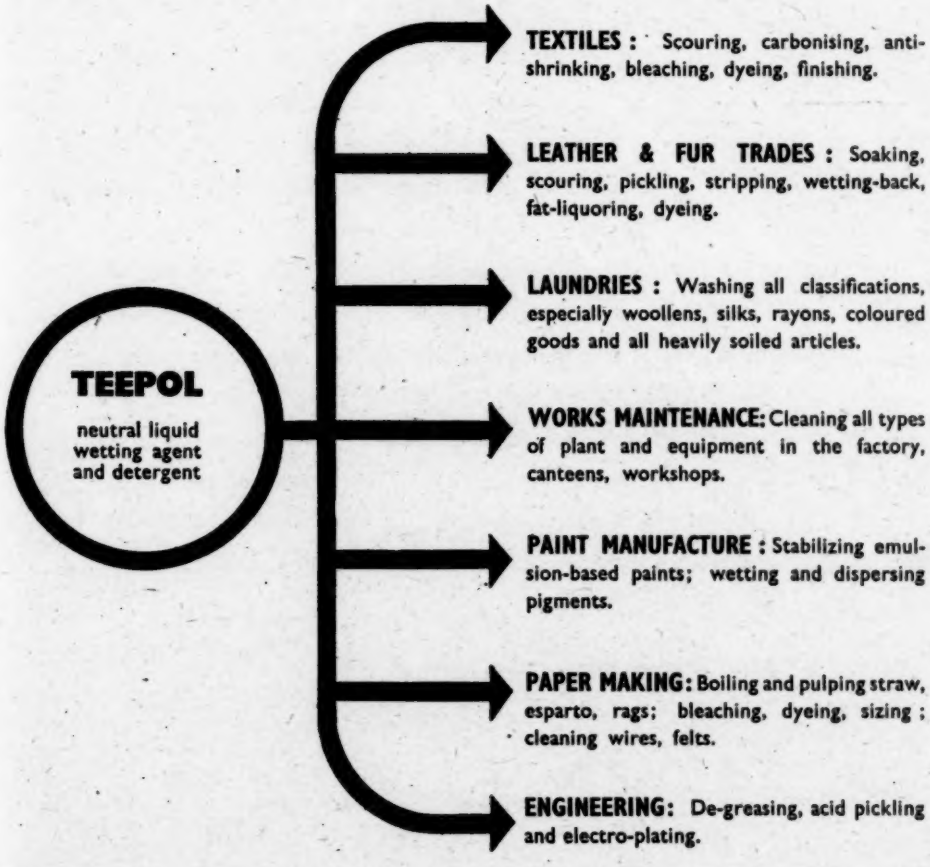
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